UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

UNITED STATES OF AMERICA,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civil Action No. 99-CV-2496 (GK)
	)	
PHILIP MORRIS USA INC. (f/k/a PHILIP MORRIS INCORPORATED), *et al.*	)	
	)	
Defendants.	)	

JOINT DEFENDANTS' WRITTEN DIRECT EXAMINATION OF PETER P. ROWELL, Ph.D.

SUBMITTED PURSUANT TO ORDER #471

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I. INTRODUCTION AND SUMMARY OF OPINIONS

Q: Please state your name for the record.

A: My name is Peter P. Rowell.

Q. Is JD-012611 a copy of your current curriculum vitae?

A. Yes.

Q: What is your current professional position?

A: I am the Associate Dean for Research and a Professor of Pharmacology and Toxicology at the University of Louisville School of Medicine.

Q: Do you have a particular focus in your research and teaching?

A: My research emphasis has been on the pharmacology of nicotine. I have developed nicotine pharmacology expertise over the last 34 years, and I have taught pharmacology at the University of Louisville for the last 28 years.

Q: About what topics have you been asked to testify?

A: First, I have been asked to address whether certain tobacco company documents identified by the plaintiff's witnesses in this case indicate that the tobacco companies knew about properties of nicotine that were unknown in published literature. Second, I have been asked to address whether, based on laboratory data, nicotine, as a drug, is different than hard drugs.

II. BACKGROUND AND EXPERTISE

Q: Dr. Rowell, please describe your background. Where are you from?

A: I was born and raised in St. Petersburg, Florida. I received my undergraduate degree from Stetson University in 1968, where my Major was Behavioral Psychology and my Minor was Chemistry. After graduation from Stetson, I entered the Army as a Second Lieutenant in the Medical Service Corps.

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Q: What did you do in your service in the Medical Service Corps?

A: I was Headquarters Company Commander at the M.A.S.H. unit in Ft. Meade, Maryland from 1969-70. I was promoted to 1st Lieutenant in 1970 and served as Platoon Leader of the medical platoon, 502nd Infantry Battalion, 101st Airborne Division in Viet Nam from 1970-71. I was stationed at the most forward permanent medical station in the region, at a "fire base," where I assigned medics and supplied equipment and training, to infantry in the field.

Q: Did you receive any commendations for your service in Viet Nam?

A: Yes, I received the Bronze Star and Combat Medical Badge, among others.

Q: Under what circumstances were you discharged?

A: I received an honorable discharge in 1971.

Q: What did you do after you left the Army?

A: After leaving the Army, I went to graduate school at the University of Florida School of Medicine in the Department of Pharmacology and Experimental Therapeutics, where I received my Ph.D., with honors, in 1975.

Q: Were you interested in nicotine pharmacology in graduate school?

A: My interest in nicotine pharmacology started in graduate school. I studied under Dr. George Chiou, currently the Chair of Pharmacology at Texas A&M, who performed some important work in nicotine pharmacology in the late 1960s and early 1970s. Dr. Chiou's work made important advances showing nicotine releasing acetylcholine from nerve terminals.

Q: Where did you do your post-doctoral work?

A: I was a Research Associate at Vanderbilt University School of Medicine in the Department of Pharmacology from 1975 to 1977. I investigated whether nicotine consumed by

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smoking expectant mothers affected the nutrients available to their fetuses, and I concluded that nicotine is not responsible for any change in amino acid transport from mother to fetus.

Q: When did you move to the University of Louisville?

A: Immediately after my post-doctoral work at Vanderbilt, I went to the University of Louisville School of Medicine as an assistant professor. I was promoted to associate professor with tenure in 1983 and to professor in 1992. My responsibilities since coming to the University of Louisville have included teaching medical, dental, advanced nursing and graduate students, and scholarly research in the area of nicotine pharmacology.

Q: Have you served on faculty committees during your time at the University of Louisville?

A: Yes. My committee service is included in my CV. My most recent appointments have included Chairman of the Promotion, Appointment and Tenure Committee at the School of Medicine, Chairman of two medical school accreditation committees, and I currently serve as an Associate Dean of the medical school.

Q: Are you affiliated with any professional organizations?

A: Yes. I am affiliated with the American Society for Pharmacology and Experimental Therapeutics; the Society for Neuroscience; the American Society for Neurochemistry; the International Society for Neurochemistry; the International Brain Research Organization; the Society for Research on Nicotine and Tobacco (charter member); the World Federation of Neuroscience; the Southeastern Pharmacology Society; the Kentucky Academy of Science; Sigma Xi; and the Louisville Chapter of Neuroscience (charter member).

Q: Are there requirements for admission to some of these organizations?

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A: Yes. For membership in the Society of Neuroscience, the American Society for Pharmacology and Experimental Therapeutics, and the American and International Societies of Neurochemistry, one must be nominated; have the most advanced degree in the field; and have an acceptable publication record.

Q: Why did you decide to take a position at the University of Louisville?

A: My nicotine expertise was key. A Kentucky state tax on cigarettes is earmarked to fund grants for basic science research on smoking and health through an institute called the Kentucky Tobacco and Health Research Institute. The University of Louisville pursued me in hopes of obtaining those research grants. Nearly all of my research during my first 15 years at the University of Louisville was funded by Kentucky Tobacco and Health Research Institute grants. In recent years, however, the vast majority of my research has been funded by the federal government, through grants from the National Institute on Drug Abuse (NIDA).

Q: Have you published peer reviewed articles and books in your field?

A: Yes. I have published about 50 original peer-reviewed scientific articles, as well as several book chapters. I have also published over 50 shorter communications and abstracts.

Q: What would you list as important research that you have published in the field of nicotine pharmacology?

A: I would point to my 1983 study of nicotine distribution, exhibit JD-011618, which presented the procedure for chronically administering nicotine to experimental animals.

I would also point to my 1984 study showing, for the first time, a nicotinic autoreceptor function on nerve terminals in the brain, which is at exhibit JD-010823. This article was cited by the Surgeon General in his 1988 Report.

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Third, I would list the first study to show nicotine-stimulated dopamine release directly from nerve endings in the brain's "pleasure center," the nucleus accumbens. This is exhibit JD-010743, published in 1987.

Fourth, I would list the first experiments demonstrating the ability of very low concentrations of nicotine to both desensitize and stimulate nicotine-evoked dopamine response from nerve endings. These studies, published in 1994-95, are shown in exhibits JD-010811 and JD-010741.

Finally, I would point to my research, published in 1997, in exhibit JD-011617, examining the correlation between nicotine-induced receptor desensitization and up-regulation in the brain.

Q: Was any of this research accomplished at or after the time that you were contacted by representatives of the tobacco companies?

A: I was first contacted by representatives of the tobacco companies in the Spring of 1995. The research for all of these studies, with the possible exception of the last one, was completed prior to that date.

Q: Dr. Rowell, were any of the studies you just listed, or any other research where you were the principal investigator, funded by any tobacco company or tobacco industry group?

A: No.

Q: Was any other work in which you have been involved, even peripherally, been funded by any tobacco company or tobacco industry group?

A: I have worked in labs where the primary researchers apparently have received tobacco money. Dr. Sastry at Vanderbilt and Dr. Susan Wonnacott in the U.K. both published, with

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myself as a secondary or tertiary author, and attributed grants from tobacco companies or CTR as funding sources in the published papers. I had no knowledge of this funding at the time and had no control over how the money was spent.

Q: Apart from your involvement as an expert in litigation, have you ever done any type of work for any tobacco companies?

A: The first and only work I have done for tobacco companies (before becoming involved as an expert in litigation) was a literature review, conducted along with Dr. Lawrence Carr, of published scientific articles on nicotine. This project, culminating in the writing of the report, helped me trace and further understand the evolution of scientific knowledge regarding nicotine pharmacology. The report that I authored with Dr. Carr was completed in 1997 and is entitled a "Historical Review of Nicotine's Actions." It is shown in exhibit JD-010797.

Q: Who asked you to do this literature review?

A: A lawyer at the Jones Day firm.

Q: What, specifically, were you asked to do?

A: I was asked to review the published literature on nicotine research and to write an historical review of that research.

Q: How many articles did you review?

A: Dr. Carr and I read over 1,000 articles; we cited several hundred in the historical review.

Q: When did you do this literature review?

A: We began the literature review in May of 1995 and completed the review at the end of 1996. So, Dr. Carr and I took almost two years to complete the review.

Q: Did the lawyers who asked you to conduct the literature review read your report?

A: Yes.

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Q: Did they suggest any substantive changes?

A: No.

Q: Did the lawyers influence your report in any way?

A: No.

Q: Did you receive personal income from the tobacco industry for your literature review?

A: No. I received no personal income from the tobacco industry. All payments for my work on the literature review were made to the University of Louisville Research Foundation.

Q: Have the payments for all of your work on tobacco litigation gone to the University of Louisville?

A: No, not all of the payments. After several years, I began billing for my time, personally. I began to accept personal compensation for my work part-way through the Minnesota Attorney General case in 1998.

Q: How much have you been paid, in total, for your work on tobacco litigation?

A: As of the end of 2004, I have been paid approximately $175,000 for my work on tobacco litigation.

Q: What is your hourly rate?

A: My current rate is $300 an hour.

Q: Aside from the literature review, have you been asked to do any other work by the tobacco companies in preparation for your expert testimony in tobacco litigation?

A: I was asked to review certain internal documents of the defendants. These documents were provided to me by attorneys representing the defendants -- some that they identified and some that I asked be given to me. I understand that the documents selected for my review by the

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attorneys appear to be documents that plaintiffs, or plaintiffs' experts, have identified as important in evaluating the research methodology and findings at the companies.

Q: What were you looking for when you reviewed these internal documents?

A: I was determining whether the documents reflect any breakthroughs in methodology or findings regarding nicotine pharmacology. The historical review of published literature that I performed with Dr. Carr formed the foundation for my critique of the internal company documents, even though I had not seen any internal documents at the time I was doing the historical review.

Q: When were you asked to review these internal documents?

A: Some time around the holidays of 1996, just after the completion of the literature review, we were asked to look at documents.

Q: How was it determined which documents you were to review?

A: I received batches of documents concerning four tobacco companies from lawyers representing those companies. The documents had been identified in upcoming attorneys general litigation by the states' attorneys general as important documents indicating some new or interesting information on nicotine pharmacology.

Q: Were you satisfied that you were given all company documents relevant to a complete review of the topic of nicotine pharmacology?

A: In the course of my review, it appeared that the attorneys had cast a wide net, because many of the documents had a tenuous relationship to nicotine pharmacology. Nonetheless, in 1999, I looked at the tobacco resolution website to assure myself that there were no significant documents relating to nicotine pharmacology that I had not seen.

Q: What did you discover in your review of these internal company documents?

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A: First, most of these documents do not reflect scientific research, data acquisition, sound experimental studies, or quantitative analysis, but rather the opinions or hypotheses of the authors regarding certain actions of nicotine. Therefore, these opinion documents did not play a role in my search for studies or science regarding nicotine.

Second, the pharmacological research by the defendants, as presented in the documents that I reviewed, do not show that the defendants had knowledge of any "addictive" properties or mechanisms of nicotine, ahead of the public scientific community.

Q: Have you testified for cigarette companies prior to your involvement in this case?

A: Yes. I have testified for the defense in three previous trials: the Minnesota A.G. case, on April 16 and 17, 1998; the Ohio Ironworkers case, on March 8, 1999; and the Gloria Scott case, on April 29, 2003. I have given depositions on March 26, 1997 for the Mississippi A.G. case; on May 7, 1997 for the Florida A.G. case; on August 26 and 27, 1997 for the Minnesota A.G. case; on September 16, 1998 for the Oklahoma A.G. case; on December 12, 1998 for the Ohio Ironworkers case; on March 6, 2000 for the National Asbestos Workers, Falise, and Blue Cross/Blue Shield of New Jersey cases; on October 19, 2000 for the West Virginia Blankenship case; on October 24, 2000 for the Louisiana Scott case; on January 8, 2002 for the California Lucier case; on April 26, 2002 for the California "Alan Harvey" case; on September 11 and 12, 2002 for this "United States" case; on October 22 & 31, 2002 concurrently for three cases: the "Roach, Welch, and Thompson" cases; and on August 15, 2003 for the Illinois "Julie Turner" case.

Q: Summarize, please, the basis for your testimony in this case.

A: I have, in my professional experience over more than 30 years, gained extensive knowledge and experience about the effects of nicotine in the body and how nicotine compares

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with other psycho-stimulant drugs such as cocaine, amphetamine, and caffeine. I am quite familiar with the neurochemistry of these drugs and the similarity and differences among them. This knowledge, coupled with my education, training and experience in psychology and pharmacology as well as my familiarity with the scientific literature on nicotine and smoking, is the basis for my conclusions regarding the effects of nicotine in the body, and the spectrum of drug and behavioral dependence.

The basis for my opinions concerning the state of scientific knowledge regarding nicotine derives from my literature review with Dr. Carr, and from my review of many thousands of pages of documents produced by tobacco companies, which have been identified as containing relevant information about nicotine and smoking. On the basis of the information I have reviewed, I am prepared to testify about the relevance and significance of the reports and various statements made by employees of the tobacco industry as they relate to understanding the actions of nicotine or smoking behavior.

Q: Have you reviewed any of the testimony in this case in preparation to testify?

A: I have reviewed the expert reports, the written direct examinations of, and portions of the live trial testimony of Doctors Benowitz and Henningfield. I have also reviewed portions of the testimony of the following witnesses: Farone, Burns, DeNoble, Mele, and Wigand. I have also reviewed documents identified by these and other witnesses relating to nicotine pharmacology and addiction.

Q: Why did you not review all of the testimony of Farone, Burns, DeNoble, Mele and Wigand?

A: I was asked to review sections of their testimony that were relevant to the issues I was asked to address in this case.

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Q: What is your area of expertise?

A: My area of expertise is in nicotine pharmacology and the history of research into nicotine pharmacology, including the connection of nicotine pharmacology to smoking behavior.

Q: What have you concluded in your work as an expert in this case?

A: First, as to the specific allegations that there was significant information concerning nicotine pharmacology known to the tobacco companies but not found in published literature, I find those allegations to be untrue. Second, I have determined that there are pharmacological differences between nicotine and hard drugs. Nicotine is a relatively weak drug. This is not to say that cigarette smoking is not compulsive, nor is it to say that cigarette smoking is easy to quit. But, nicotine, as a drug, is not the only factor involved in cigarette smoking behavior.

Q: Are you an expert in smoking behavior?

A: I am not an expert in "smoking behavior" per se, but nicotine pharmacology overlaps with smoking behavior, because nicotine pharmacology looks at properties of nicotine as a drug that may account for smoking behavior.

Q: Have you been asked to address the topic of smoking compensation in this case?

A: No.

III. ANALYSIS OF HISTORICAL DOCUMENTS IN RELATION TO EXTERNAL SCIENCE

Q: Now, Dr. Rowell, I would like to turn to your review of company documents and the historical record of scientific research concerning nicotine pharmacology and addiction. Are you prepared to address that topic?

A: Yes.

Q: I am going to direct your attention to three time periods relevant to this discussion: first, the period prior to 1964, the year when the U.S. Surgeon General published a report

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on "Smoking and Health"; second, the period between 1964 and 1988; and finally, the period after 1988, the year when the U.S. Surgeon General published the report on "Nicotine Addiction." In your view, is this a reasonable separation of time periods?

A: Yes.

A. Analysis of Company Documents and External Science pre-1964

Q: Let's look, first, at the period prior to 1964.

A: All right.

1. Early Pharmacological Investigation of Nicotine

Q: Dr. Rowell, can you briefly summarize the early pharmacological investigation of nicotine?

A: Yes. Pharmacological investigation of nicotine has gone on for approximately two centuries. The early research focused on the isolation of nicotine and the initial recognition of nicotine's pharmacological effect. Once the pharmacological effect of nicotine was recognized, further research on that topic ensued.

a. Isolation of Nicotine

Q: When was nicotine, as a component of tobacco, "discovered"?

A: In the early 1800s Vauquelin determined that many of tobacco's physiological effects were due to the presence of a potent alkaloid in tobacco preparations, which he named "nicotine," after his countryman, Jean Nicot. Isolation of the pure alkaloid was accomplished soon thereafter.

b. Early Research Into Nicotine's Pharmacological Effects

Q: When were the first studies on nicotine's physiological effects performed?

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A: In pioneering experiments in 1889, Langley and Dickinson, as shown in JD-030091, demonstrated that administration of small doses of nicotine could stimulate autonomic ganglia in the peripheral nervous system, whereas large doses caused blockage of ganglionic transmission. Studies using nicotine, at the turn of the last century, were fundamental to discovering how nerves communicate with each other by acting on a "respective substance" (now called a "receptor") on the adjacent nerve. The first receptor discovered, and the first one isolated and characterized, was named after nicotine. It is now called the nicotinic receptor.

While these studies at the turn of the century were the first physiological studies done on nicotine, it is worthy of note that the fact that nicotine is in tobacco, and that nicotine has "drug effects" on the nervous system and contributes to continued smoking, has been known for centuries. Dr. Henningfield, one of plaintiff's experts in this case, has noted in JD-000975, that the American Indians knew, centuries ago, that tobacco had "psychoactive" properties such that it altered moods and feelings.

Q: When did the scientific community first begin to understand the bond between tobacco and the smoker?

A: The 1988 Surgeon General Report on Nicotine and Addiction, U.S. Ex. 64,591, recited that "[a]s early as the 1920s and 1930s, some investigators were concluding that nicotine was responsible for the compulsive use of tobacco products."

Q: Did the pharmacological research on nicotine prior to 1964, recognize nicotine as a reason for smoking?

A: Yes. An article, JD-000972, published over 50 years ago in Lancet, a British medical journal widely considered among the most authoritative in the world, characterized smokers as nicotine addicts.

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> On the assumption that smoking tobacco is essentially a means of administering nicotine, just as smoking opium is a means of administering morphine, nicotine was given hypodermically to 35 volunteers in known doses with a view to comparing its effects. . . . Smokers show the same attitude to tobacco as addicts to their drug, and their judgment is therefore biased in giving an opinion of its effect on them.

Moreover, additional research on nicotine as a reason for smoking is cited in Larson, Haag and Silvette's encyclopedic review of studies on nicotine pharmacology, JD-000500. Larson at page 526, cites to a study by Gies et al. which "conclusively demonstrated during World War I that cigarettes made wholly or in part of other plants did not exercise a tranquillizing influence on tobacco smokers, nor satisfy their acquired fondness for mild forms of tobacco."

2. Use of the Term "Addiction" in the External Literature

Q: What was said about "addiction" during this time period in the scientific community?

A: Use of the term "addiction" to describe the habit-forming qualities of nicotine was frequently in the scientific and public health literature during this time period.

Q: Can you give some examples of use of the term addiction during this time period?

A: Peter Knapp in 1962 published an article entitled "Addictive Aspects in Heavy Cigarette Smoking," JD-000298, and wrote at page 966, that tobacco "appears to have certain addictive qualities," noting tolerance development, in particular. This work was sponsored by the tobacco industry. Additionally, Dr. Henningfield noted in his 1984 chapter on "Behaviorial Pharmacology of Cigarette Smoking," JD-010831, that "[S]cholars of the seventeenth and eighteenth centuries wrote of the addictive nature of smoking and drew comparisons between tobacco, opium, and alcohol use."

Q: In the period prior to 1964, did some researchers also call cigarette smoking a habit, rather than an addiction?

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A: Yes. Some researchers referred to smoking as a habit. For example, exhibit JD-010777 is an article from 1927 by Dixon, entitled "The Tobacco Habit," which states:

> Habitual smokers are agreed that the weed acts as a mild sedative to the central nervous system; the type of action is of a somewhat remarkable character and may offer an explanation of the widespread use of tobacco.

Similarly, exhibit JD-000499 is a 1945 article by Finnegan entitled "The Role of Nicotine in the Cigarette Habit", which stated:

> It would seem clear from these results that with many individuals nicotine becomes a major factor in their cigarette habit. Equally certain, with many individuals nicotine is not a factor in their cigarette habit.

Q: Are you familiar with the British Royal College of Physicians?

A: Yes, it is similar to the U.S. Surgeon General's Office in Great Britain.

Q: What terms did it use to discuss smoking behavior?

A: The Royal College of Physicians issued a report in 1962, U.S. Ex. 21,023, entitled *Smoking and Health*, which noted the "[w]idespread popular beliefs (which doctors mostly share) . . . that it [smoking] is, or at any rate can become, an addictive habit." The Royal College of Physicians used the terms "habit" and "addiction" with no real precision:

> The discomforts that ensue when smoking is stopped may thus be genuine withdrawal symptoms due to addiction to nicotine, but are also those to be expected when any well-established and pleasant habit is discontinued, particularly one which has become a valued element in everyday life and is regarded as a prop or solace.

Q: In the United States, did researchers begin to discriminate between the terms "addiction" and "habit" in the time period prior to 1964?

A: In 1962, as is evident in JD-010715, Professor Maurice H. Seevers, who later became a member of the Surgeon General's Advisory Committee with responsibility for pharmacological questions, including habituation and addiction, recognized the views of those who claimed that

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nicotine was "addictive," but felt that such a classification of nicotine had no basis in "scientific fact." Seevers determined that the confusion concerning the labeling of smoking behavior was not new, and was worse in 1962 than in the past.

3. Tobacco Company Research

Q: Were the tobacco companies doing research, in the period prior to 1964, on the pharmacological effects of nicotine?

A: Yes.

Q: Does your review of company documents indicate that any of the companies -- prior to 1964 -- had knowledge about the pharmacological properties of nicotine ahead of the external research?

A: No.

a. Medical College of Virginia

Q: Can you give some examples of company research in the time period prior to 1964?

A: Significant work was done by the Medical College of Virginia, also know as the "MCVA," sponsored by the American Tobacco Company, and by Battelle for British American Tobacco Company, known as "BATCo."

Q: Please describe the work done at the MCVA.

A: Prior to 1964, extensive work regarding the pharmacological effects of nicotine was performed at the MCVA. The American Tobacco Company sponsored biological research at the MCVA for approximately 40 years, between July 1936 and July 1975. This program focused on biological, chemical, and physiological research.

Q: Was the MCVA research published?

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A: Yes. The American Tobacco Company periodically published pamphlets summarizing for the public its research activities at the MCVA, ultimately listing 112 publications by the MCVA researchers. JD-010314 is a compilation of those MCVA publications.

Q: Was the MCVA involved in any other work concerning nicotine pharmacology?

A: In addition to its ongoing research, the MCVA collected and reviewed published studies on the effects of nicotine and tobacco constituents generally. This led to the 1961 publication of one of the world's definitive sources on tobacco: *Tobacco: Experimental and Clinical Studies* by Larson, Haag and Silvette, JD-000500. Based on more than 6,000 references to scientific articles on biologic effects of tobacco and its constituents, Larson's encyclopedic volume, which has been supplemented three times since publication, presents knowledge on all aspects of the biologic effects of tobacco and nicotine.

Q: Can you briefly describe some of the topics covered in the 1961 Larson text?

A: The Larson text covered topics ranging from the absorption and fate of nicotine in the body; the effect of nicotine on the nervous system, on skeletal muscle, on blood, on the cardiovascular system, on the respiratory system, on the urinary tract, and on the gastrointestinal tract. Larson's text also covered toxicology, tolerance, the tobacco "habit," and the relation of tobacco use to specific diseases. This listing is by no means complete.

Q: Who funded Larson's text?

A: Larson's text and its supplements, as noted in the Preface to the volume, were funded by the Tobacco Industry Research Committee, also known as the "TIRC."

Q: Do respected authorities rely on the Larson text?

A: Yes. The Public Health Service has relied on the Larson, Haag & Silvette text (and its several supplements) as an authoritative summary of the world's smoking and health literature.

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Q: Has the Surgeon General's office relied on the Larson text?

A: The Surgeon General's Advisory Committee, known as the "SGAC," in 1964 relied on this co-funded project for its observations regarding the published smoking and health literature pre-1959. The 1964 Surgeon General's Report acknowledges Larson in the acknowledgement section of the report. Several subsequent Surgeon General's reports relied on and cited the Larson text.

Moreover, on page 14, the Surgeon General's Advisory Committee notes:

> As the primary duty of the Committee was to assess information about smoking and health, a major general requirement was that of making the information available. That requirement was met in three ways. The first and most important was the bibliographic service provided by the National Library of Medicine. As the annotated monograph by Larsen, Haag, & Silvette -- compiled from more than 6,000 articles published in some 1,200 journals up to and largely into 1959 -- was available as a basic reference source, the National Library of Medicine was requested to compile a bibliography (by author and by subject) covering the world literature from 1958 to the present.

b. Work by Battelle (Sponsored by BATCo)

Q: You mentioned pharmacology work done by Battelle for BATCo in the period prior to 1964. What was the topic of the Battelle research?

A: BATCo, through contract with the Battelle Research Institute, was studying the properties of nicotine in the early 1960s.

Q: What research was conducted by BATCo prior to 1964?

A: In 1959, BATCo contracted with Battelle Geneva to conduct preliminary pharmacology research on the physiological and psychological effects of smoking, and to explore the possibility of obtaining the same results by a device other than a cigarette.

Q: Why was BATCo interested in pursuing this research?

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A: In the 1950s, the tar in cigarette smoke was under attack by scientists and others as the alleged cause of disease in smokers. The Battelle research was motivated by BATCo's desire to eliminate tar in its products and provide a "safer" smoke. A 1962 document, a "Proposal for Further Research Contracts with Battelle," JE-046579, states that the overall objective of the Battelle research was to increase knowledge about the effects of smoking and to explore whether those same effects could be had by a device other than a cigarette. The proposal states that "some device which delivered the nicotine in an acceptable form without the harmful combustion products would be possibly more desirable."

Q: Is the Battelle research documented?

A: The Battelle research generated a series of reports and papers in the early 1960s under the names Project Hippo and Project Mad Hatter, which I reviewed in the course of my review of company documents.

Q: What was Project Hippo?

A: There were two Hippo Projects -- Project I and Project II. Project Hippo I, U.S. Ex. 20,247, was a rat study, which was started in 1961 by researchers at Battelle, designed to investigate the physiological effects of nicotine on certain body functions: urine production; production of adrenocorticotrophic hormone, also known as "ACTH"; regulation of body weight and free fatty acids; and the production of thyroid stimulating hormones.

Q: What conclusions were reached in Hippo I?

A: Project Hippo I reached the following conclusions:

- Nicotine acts as an antidiuretic in unexposed rats. This effect declines in nicotine exposed rats.

- Nicotine enhances the rat defense mechanism against stress by stimulating the release of ACTH.

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- Nicotine inhibits weight gain by stimulating the release of free fatty acids, also known as "FFA", and degrading lipids.

- Battelle failed to find an effect on the hypothalamic function.

Q: What was Project Hippo II?

A: Project Hippo II, U.S. Ex. 20,246, was a study by Battelle researchers that investigated the biochemical effects of nicotine on the brain and compared them with reserpine, a well-known tranquilizer. The first, or preliminary, report was issued in June 1962, and the final report in April, 1963.

Q: What conclusions were reached in Hippo II?

A: Most importantly, Project Hippo II concluded that "Our attempts to explain nicotine activities on brain functions on a biochemical basis was not successful." In support of that conclusion, the researchers determined that:

- Contrary to the Battelle hypothesis, nicotine did *not* deplete serotonin levels in the brain like reserpine did.

- Reserpine, unlike nicotine, does not enhance the pituitary-adrenal response to stress (ACTH release) and does not regulate body weight.

Q: You mentioned Project Mad Hatter. What was that?

A: "The Fate of Nicotine in the Body," U.S. Ex. 21,562, was a report issued in May 1963 as part of Project Mad Hatter. More specifically, it was a study of nicotine absorption, distribution, metabolism, and elimination performed in human volunteers, rats, and rabbits.

Q: What were the conclusions of Project Mad Hatter?

A: The study reached the following conclusions:

- Inhaling smokers absorb more than 70 percent, even up to 90 percent, of nicotine drawn into the mouth. Smoking habits can influence the amount of nicotine drawn into the mouth.

- Radio-labeled nicotine in rabbits is metabolized by enzymatic breakdown that begins immediately. It is also quickly removed from the blood stream.

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- Smoke inhalation results in blood absorption of nicotine almost as rapidly as intravenous injection.
- Nicotine is effectively eliminated from the body and does not accumulate in tissues.
- No behavioral measurements were made in this experiment.

Q: Were any of the conclusions of Project Hippo I or II novel?

A: No. Battelle's conclusions in the Project Hippo I and Project Hippo II reports were not new or unique. There was comparable research published at or before the time the Hippo reports were issued by Battelle in 1961 and 1962.

Q: What external research was published at or before the time of the Hippo reports that was comparable?

A: Comparable external research was well documented in the Larson Text, JD-000500, as shown by the following examples:

- The antidiuretic effects of smoking were known, as shown, for example, in publications by Burn and Maren (1951).
- The effects of smoking on body weight were known, as shown, for example, by JAMA in 1942, and in a 1952 study by Essenberg, JD-061362.
- The effect of nicotine on the level of free fatty acids was known, as shown, for example, in a 1953 article by Walker.
- The effects of nicotine on ACTH were known, as shown, for example, in a 1955 article by Venulet and Majcherski.

Q: Were any of the conclusions of Project Mad Hatter new?

A: No. Battelle's Fate of Nicotine in the Body research was comparable to contemporaneous, published science. Studies examining the absorption, distribution, metabolism, and elimination of nicotine were published in the 1950s and 1960s as recited in the first 27 pages of the 1961 Larson text, JD-011834. Moreover, as already explained in reference to the Hippo reports,

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- The antidiuretic effects of smoking were known.
- The antidiuretic and adrenocorticotrophic effects of nicotine were known.
- The effects of smoking on body weight were known.
- The effect of nicotine on the level of free fatty acids was known.
- The effects of nicotine on ACTH release were known.

Q: What was BATCo's reaction to the results of the Hippo work?

A: While fully appreciating the beneficial qualities of nicotine, Sir Charles Ellis raised concerns regarding the preliminary nature of the work done in the Hippo reports. In May 1963, Ellis recommended in a memo to BATCo Chairman Duncan Oppenheim, JD-010695, that Hippo I and II be sent to The Tobacco Research Council, also known as the "TRC." As is clear from this memo, Ellis thought that the results on the benefits of nicotine might help the industry's public position and that the TRC should review the Project Hippo reports to determine their scientific worth. Ellis was reluctant even to send the research to other Group companies, stating that there was "little point in sending" the Hippo research before it "had survived the critical appraisal of our own experts in this country." Even if the TRC did find that the Hippo research had scientific value, Ellis concluded that more work would have to be done before publication of the results: "The question of publication in a scientific journal scarcely arises at this stage since the results have not been written up for that purpose."

Q: What was the TRC?

A: The Tobacco Research Council or "TRC" was an organization funded by the tobacco industry in the United Kingdom that supported scientific research related to the health effects of tobacco. The TRC both established relationships with outside scientists and ran its own laboratories to research issues related to smoking and health. The TRC regularly publicized its

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research program in reports, called Reviews of Activities, and by the publications in scientific journals of its own researchers and of grantees who received TRC funding.

Q: Did Ellis send the Hippo reports to the TRC?

A: Ellis subsequently sent the Hippo reports to Dr. Todd, Director of the TRC. In the cover letter accompanying the reports, U.S. Ex. 85,387, Ellis reiterated his belief that the Hippo reports should be kept "strictly confidential until . . . the results have been critically reviewed by the T.R.C. scientific experts." Ellis also expressed his view in the letter that nicotine had many beneficial effects and that these beneficial effects should be publicized.

Q: What did the TRC determine about the value of the Hippo reports?

A: Two TRC scientists, Doctors Armitage and Burn, issued two "appraisal reports," determining the scientific value of the Project Hippo and Project Mad Hatter research and concluded that the Hippo and Mad Hatter research suffered from many methodological flaws, was preliminary in nature, and was not of publishable quality. Dr. Armitage was the head of the TRC's pharmacology department, and was a famous researcher on nicotine in the 1960's and the 1970's. Dr. Burn was also one of the TRC's consulting pharmacologists.

Q: What specifically did Drs. Armitage and Burn conclude about Hippo I and II?

A: Drs. Armitage and Burn authored a detailed appraisal of Hippo I and Hippo II's first and final reports, observing that there were many flaws in the methodology of the studies, and that the results were merely preliminary. They concluded that "[t]he information in these reports is not sufficiently complete to justify any form of publication," and included the following observations concerning Project Hippo in JE-047067:

- The data are "poorly presented by any standards" and "the experiments are in some cases impossible to follow."

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- Dr. Libert, who did most of the work at Battelle, is an endocrinologist, not a pharmacologist or biochemist.

- Rat procurement (no litter-mate controls) and animal accommodations were poor.

- Apparently, no non-nicotine controls were used in the water excretion testing.

- Armitage stated that Battelle's conclusion that nicotine does not stimulate the hypothalamic center is wrong and that, during his visit to Battelle's laboratory, Dr. Libert agreed with him.

- The absence of litter-mate controls suggested that the weight regulation tests were "of doubtful significance." Also, there was no control for effect on appetite caused by injection trauma.

Q: What, specifically, did Drs. Armitage and Burn conclude about Project Mad Hatter?

A: Dr. Armitage drafted an appraisal report of Project Mad Hatter, similar to the one he had co-authored with Dr. Burn evaluating Project Hippo. He made the following observations in JD-010719:

- Others had tested with machines the amount of nicotine drawn into the mouth. Those published results were significantly lower than Battelle's (*e.g.,* 0.9 - 2.4 mg. versus 4 - 5.5 mg.), which raised concerns about Battelle's test methods.

- The animal metabolism studies largely replicated previously published work.

- Armitage critically noted Battelle's own statement that its data offer nothing regarding a mechanism for tolerance: "This important problem was, I imagine, the main object of the research."

Q: How did BATCo respond to the evaluations of Drs. Armitage and Burn?

A: These evaluations convinced Sir Charles Ellis that the Hippo and Mad Hatter projects suffered from many methodological flaws and that the results were too preliminary to be submitted to the Surgeon General's Advisory Committee in 1963. After Ellis reviewed the appraisal report of Armitage and Burn, he reportedly agreed, as recorded in JD-032033, which is a July 3, 1963 "incoming cable", that "further investigation [was] desirable before publication."

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Ellis concluded that there were many flaws in the Hippo and Mad Hatter research. For example, a letter from Battelle to Ellis written in February, 1964, JD-010717, quotes Ellis as stating:

> The impetus of HIPPO work has helped the tobacco industry to take a positive attitude to the beneficial effects of nicotine. We have used the general results of this work repeatedly in this direction, and as regards BAT/Battelle we are entirely satisfied.
>
> We are aware, however, that it is difficult to maintain the scientific value of HIPPO work against skilled criticism.

Q: So, did BATCo submit the Hippo research to the Surgeon General's Advisory Committee?

A: As a consequence of the methodological flaws inherent in the Hippo research and the preliminary nature of the work, Ellis and BATCo were reluctant to submit the Battelle reports to the Surgeon General's Advisory Committee in 1963. Ellis appeared concerned that such a submission would appear to be promoting the benefits of nicotine based on flawed research. Accordingly, as reflected in JG-054272, Ellis advocated not taking the initiative in submitting the reports to the committee, but rather advised that B&W "wait and hope that the Committee will ask the individual manufacturers for further details of their research work and then . . . submit the Battelle work. . . ." Ellis believed that if the reports were submitted in response to a request, "the work would be immune from detailed criticism" since "further work" had to be done.

c. Use of the Term "Addiction" in Company Documents

Q: In the time period prior to 1964, did some documents call nicotine "addictive"?

A: At the time the Hippo research was being done, references appeared in some BATCo and Battelle documents describing nicotine as "addictive." These references do not differ from those being made in the open scientific literature at that time.

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Q: Can you recall examples of use of the term "addiction" in company documents that you reviewed?

A: Yes, the company documents generally reflect the confusion of terminology from the published scientific reports. For example, as reflected in JE-053468, at a BATCo research conference in Southampton shortly after the 1962 Royal College of Physicians Report issued, BATCo scientist Sir Charles Ellis picked up the same confusing terminology of the Royal College report, and thus termed smoking a "habit of addiction."

Q: Do any documents reflect whether Ellis believed that nicotine was "addictive" like other drugs of abuse?

A: Despite Ellis' imprecise use of the term "addiction," Ellis explicitly stated on many occasions that nicotine was not addictive like tranquilizers, sleeping pills, and hard drugs such as morphine. For example, even before the TRC issued its appraisal report on Project Hippo, Ellis concluded, in JD-010695, which was a May 1963 memo to BATCo's chairman, based on his preliminary review of the Battelle work, that smoking had genuine physiological benefits and that it was *not* addictive in the same way as such other substances:

> Nicotine is a wonderfully beneficent drug which does not, like morphine, sleeping pills or even dexedrine, lead to cumulative addiction.

Q: Are you familiar with a 1963 document authored by Addison Yeaman, then General Counsel of Brown & Williamson, U.S. Ex. 56,986?

A: Yes.

Q: In that 1963 memorandum, Yeaman stated that "nicotine is addictive. . . . We are, then, in the business of selling nicotine, an addictive drug effective in the release of stress mechanisms." Are you familiar with that often quoted statement?

A: Yes.

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Q: Was Yeaman's use of the term "addictive" unusual for the time -- 1963?

A: Not at all, and there is no reason to think that Yeaman used the term "addictive" in his 1963 memorandum to mean that smokers are unable psychologically or pharmacologically to quit smoking.

Q: Did Yeaman's memo link the term "addiction" with the beneficial effects of nicotine?

A: Yes, Yeaman was aware of the Battelle research and linked the beneficial effects of nicotine with the term "addiction," as Sir Charles Ellis had. Like Ellis, Yeaman believed that nicotine had many beneficial effects that should be publicized. His 1963 memorandum begins as follows:

> The determination by Battelle of the 'tranquilizing' function of nicotine, as received by the human system in the delivered smoke of cigarettes, together with nicotine's possible effect on obesity, delivers to the industry what well may be its first effective instrument of propaganda counter to that of the American Cancer Society, *et al*. . . .

Immediately above the passage in which Yeaman described nicotine as "addictive," he cited Battelle's conclusions that smoking brought a "relief of anxiety," that smoking had a "sedative" or "soothing" effect, that nicotine was "more 'beneficial'" and "less noxious" than tranquilizers, that nicotine enhanced the "pituitary-adrenal response to stress," and that nicotine helped in regulation of body weight. Thus Yeaman, like Ellis, equated nicotine's beneficial effects with "addiction" -- smokers made a decision to continue to smoke in order to derive these many benefits from nicotine.

Q: In what context was Yeaman writing his 1963 memo?

A: Yeaman's memorandum was written in the context of the Hippo II report, which he was reading and reacting to when he wrote the memorandum.

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4. The 1964 U.S. Surgeon General Report

Q: In 1964, what did the U.S. Surgeon General conclude regarding nicotine and addiction?

A: The 1964 Surgeon General's Report, U.S. Ex. 64,057, explicitly described the pharmacological effects of nicotine and the bond between nicotine and smokers. Specifically:

- The Surgeon General's Report recognized that tobacco had "biological effects" and that all "drug habits," such as caffeine and tobacco use, involved "psychogenic dependence" and a "pharmacological drive."

- The Surgeon General's Report found that tobacco did not create physical dependence and stated: "Proof of physical dependence requires demonstration of a characteristic and reproducible abstinence syndrome upon withdrawal of a drug or chemical which occurs spontaneously, inevitably, and is not under control of the subject."

- The Surgeon General's Report also stated: "In medical and scientific terminology the practice [of smoking] should be labeled *habituation* to distinguish it clearly from *addiction*, since the biological effects of tobacco, like coffee and other caffeine-containing beverages, . . . are not comparable to those produced by morphine, alcohol, barbiturates, and many other potent addicting drugs." That conclusion was based on criteria set forth in 1957 by the World Health Organization.

Q: Regarding the 1964 Surgeon General's Report, and its characterization of smoking as a "habit" and not an "addiction," Dr. Jack Henningfield, one of the Government's witnesses, testified that Project Hippo's "specific research findings in the narrow sense would not have changed the [Surgeon General's] opinion because these research findings

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did not, for example, demonstrate intoxication, abnormal personality disorder." Do you agree with that testimony?

A: I do agree. The Project Hippo reports offered no evidence that could have changed the description of smoking from "habit" to "addiction" based upon the criteria set forth in the 1964 Surgeon General's Report. The Surgeon General's conclusion that smoking was a habit and not an addiction was based on criteria set forth in 1957 by the World Health Organization. Given that the Committee employed these definitions, access to the Battelle research, which in any event was not new, would not have changed the Committee's conclusion. Therefore, even if the report had been submitted to the Surgeon General's Advisory Committee, there is no evidence that the 1964 Surgeon General's report would have concluded that smoking was not a "habit."

Q: When asked whether, in the Hippo research "the fact that the companies were making an assumption about the criticality of nicotine might have made a difference" to the Surgeon General's Advisory Committee, Dr. Henningfield responded, "Yes." Do you agree with Dr. Henningfield?

A.: No. The Hippo research demonstrated no novel science concerning nicotine. Even without the Hippo research, the Surgeon General's Advisory Committee concluded that nicotine had pharmacological activity, including CNS effects; that the pharmacological properties of nicotine were the "decisive factor" in the "effects of tobacco, desired or undesired;" and that nicotine-free plant materials "do not satisfy the needs of those who acquire the tobacco habit.". Moreover, the companies were focused on the Hippo research because of the benefits that it showed from use of nicotine. Certainly, the fact that a tobacco company thought that nicotine had beneficial effects would not have been important to the Surgeon General. Furthermore, the Surgeon General's Advisory Committee concluded that one of the pharmacological properties of

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nicotine for which people smoked was its ability to relieve stress, which was the subject of the Hippo research.

B. Analysis of Company Documents and External Science 1964-1988

Q: Now, Dr. Rowell, I want to turn to the period between 1964 and 1988.

A: All right.

1. Published Research and Company Documents on Nicotine Pharmacology

a. TRC Research on Nicotine Pharmacology

Q: During the period 1964-1986, did the tobacco industry sponsor research by external scientists on nicotine pharmacology?

A: Yes. The tobacco industry was continuing research on the pharmacological effects of nicotine through the TRC, which awarded grants to outside researchers.

Q: What research was the TRC engaged in concerning nicotine?

A: My Historical Review, with Dr. Carr, reflects a number of publications that derived from TRC activities. The TRC 1963 Review of Past and Current Activities, JD-011382, disclosed that, with guidance from BATCo, the TRC conceived of and implemented a decade's worth of nicotine pharmacology research at its laboratories in Harrogate. In 1963, the TRC publicly described its program for "research into pharmacological effects of smoking which would provide information on this subject that was valid and authoritative." It stated that it would finance this research both at its Harrogate laboratories and with grants to outside researchers. The 1963 Review disclosed the following TRC initiatives:

- Harrogate: Compare CNS effects of nicotine and a nicotine-free basic fraction to test whether other substances in smoke are active; determine whether nicotine releases adrenaline and noradrenaline; conduct direct brain injection and perfusion to test the effects of nicotine and blood-brain barrier permeability; measure nicotine levels in smoke; and study the pharmacology of nicotine transformation products.

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- London School of Pharmacology: Finance research on the effects of smoke, nicotine, and transformation products; and study the effect of nicotine on hydrocortisone levels in blood.
- University of London: Study the effects of smoking on the performance of psychological tests.

Q: Was TRC's research publicized?

A: The TRC's research program was regularly publicized in the TRC Reviews of Activities and through articles resulting from the program. Some of the research substantially duplicated the research conducted by Battelle in Projects Hippo and Fate of Nicotine in the Body. For example, the various nicotine research efforts and results that the TRC disclosed in its Review of Activities for 1963-1966, JD-010689, included the following:

- Study of ACTH release in cats.
- Nicotine dose-response tests in rats.
- The effect of nicotine on rat lever pressing activity.
- Study of elevated levels of FFA and glucose in cats.
- The effect of body weight of nicotine injections.

Q: Did TRC's research continue into the later 1960s and 1970s?

A: Yes. TRC continued to support external research on nicotine and continued to publicize its research in the TRC Reviews of Activities. The next such Review was published in 1969, covering the period between 1967 and 1969, JD-030988. In this Review, TRC Reports studies on the "development of tolerance" to nicotine in rats, sites of action of nicotine, effects of nicotine on the central nervous system of chickens, nicotine absorption and metabolism in man, effects on chemical transmitters in the brain, and synthetic agonists and antagonists of nicotine.

Q: Was another Review of Activities published by TRC after 1969?

A. Yes. TRC's "Review of Activities, 1970-74", was published next.

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Q. Does this review of activities report any nicotine research supported by TRC from 1970 to 1974?

A. Yes. For example, it reports studies on the effects of nicotine on the brain and behavior, noting that "Hall (1970) described some complex neuropharmacological studies in which he found that intravenously administered nicotine or inhaled tobacco smoke helped to maintain a state of behavioural arousal in the brains of animals" and "Hall and Turner (1972) showed that nicotine released noradrenaline from cat and rat hypothalamus and suggested that one of its actions was possibly to modify synaptic transmission in an adrenergic system."

Q: Does your Historical Review cover this research?

A: Yes, while I do not refer specifically to the internal TRC activity reviews during this period, I did review the various publications that came out of the TRC program.

b. Published Research on the Importance of Nicotine

Q: In the period between 1964 and 1988, were articles published on the importance of nicotine to the smoker?

A: Yes.

Q: Please describe the types of research reported.

A: First, beginning in the late 1960's, researchers examined whether smokers could -- and to some degree would -- "compensate" for reduced tar and nicotine by smoking differently. Much of this research was funded by the tobacco industry. For example, a 1968 article in Nature by TRC funded scientist Armitage, JD-000452, states:

> "It is worth noting that someone smoking a cigarette has literally finger tip control of how much nicotine he takes into his mouth, by reducing the puff volume or inhaling less frequently he absorbs less nicotine."

Q: Can you cite other types of research into the importance of nicotine?

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A: In 1974, for example, M.A.H. Russell in a Lancet article, JD-000836, noted that the safest cigarette is likely to be one with a low tar yield and a high nicotine yield. According to Russell, such a cigarette would minimize the amount of tar it is necessary to inhale to obtain a given amount of nicotine. In 1976, Russell noted in a publication in the British Medical Journal, JD-000841 that, "People smoke for nicotine but they die from tar." He suggested that the risk of early disease might be effectively reduced if attention were focused on how to reduce their tar intake irrespective of nicotine intake. He further suggested that the most logical way to do this would be to develop a low tar yield/medium nicotine yield cigarette with an emphasis on the ratio of tar to nicotine yield.

Q: Was M.A.H. Russell a prominent, well-respected cigarette researcher in the 1970s?

A: Yes. Russell was and is one of the most well-respected nicotine researchers in the world. He was one of the first to study issues of smoker compensation and was the first researcher to use cotinine as a biomarker for nicotine blood levels, which was an important development in compensation research. I have met Dr. Russell at conferences and scientific meetings, and recall that he was the keynote speaker at some of those conferences.

Q: Were other researchers making similar recommendations about tar and nicotine ratios at the time?

A: Yes. The concept was discussed at scientific meetings and reported in the literature. For example, the recommendation was reported by the editors of Consumer Reports. In JD-010760, the 1972 Consumers Union Report on Narcotics, Stimulants, Depressants, Inhalants, Hallucinogens, and Marijuana – Including Caffeine, Nicotine and Alcohol, "Licit and Illicit Drugs," Edward M. Brecher and the editors of Consumer Reports recommended that cigarette

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manufacturers "[d]evelop a short cigarette with *high* nicotine content, capable of delivering a maximum of nicotine to the bloodstream with a minimum of smoke to the lungs."

Q: Are you aware of any government agency at the time endorsing the idea that medium nicotine, low tar cigarettes might be safer than conventional cigarettes?

A: Yes. For example, I am aware from reading portions of Dr. Farone's live testimony that the National Cancer Institute's Tobacco Working Group suggested that the cigarette companies pursue the idea and determine whether the production of such cigarettes was feasible. Dr. Farone also testified that the Surgeon General made the same recommendation to the companies.

c. Company Documents on Nicotine Pharmacology and Smoking for Nicotine

Q: Turning to the internal documents, do you agree with Dr. Henningfield that defendants' research on pharmacological effects of nicotine showed that the companies had knowledge ahead of the outside scientific community?

A: No. Certainly the companies were doing and sponsoring research on nicotine -- as were public health authorities and scientists outside of the tobacco companies. No company documents demonstrate that company scientists had any unique knowledge of nicotine pharmacology.

(1) Company Documents Regarding Nicotine Pharmacology

Q: Dr. Kessler cited certain Reynolds' documents to support his testimony that "key industry officials knew nicotine was a drug and said it long before FDA did." [Kessler written direct 50:1-6, 59:5-8] How do you respond to that testimony?

A: It is surprising that Dr. Kessler indicated that the FDA did not realize that nicotine was a drug in the early 1970's, when some of the Company documents were written. The effects of

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nicotine on the body and the pharmacological properties of nicotine had been studied since the late 1800's, as I previously discussed. The 1964 Surgeon General's report recites these properties.

Q: Have you reviewed documents cited by Dr. Kessler?

A: Yes.

Q: For example, have you reviewed U.S. Exhibit 20,659, entitled "Research Planning Memorandum On The Nature Of The Tobacco Business And The Crucial Role Of Nicotine Therein" dated April 14, 1972?

A: Yes, I have reviewed this document.

Q: Have you reviewed U.S. Exhibit 20,708, entitled "Research Planning Memorandum on Some Thoughts About New Brands of Cigarettes For The Youth Market," dated February 2, 1973:

A: I have reviewed that document.

Q: What is your reaction to Dr. Kessler's characterization of these documents?

A: I disagree with Dr. Kessler. Like most of the tobacco companies' documents that I reviewed, they do not reflect scientific research, data acquisition, sound experimental studies, or quantitative analysis. Instead, they appear to reflect simply the opinions and hypothetical musings of Claude Teague. Furthermore, as we discussed earlier, the fact that nicotine has drug effects has been known for centuries.

Q: According to Dr. Henningfield, U.S. 20,659, described above, and a draft document prepared by Claude Teague in 1969, U.S. Exhibit 21,433, "Proposal Of A New, Consumer-Oriented Business Strategy For RJR Tobacco Company," reflect Reynolds' knowledge of the addictiveness of smoking and nicotine. Have you reviewed this document U.S. 21,433?

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A: Yes.

Q: Do you agree with Dr. Henningfield's characterization of the document?

A: No. Again, this document, like the others, appears to reflect simply the ideas of Claude Teague. It contains no scientific information, no empirical data, and no experimental studies. Therefore, his opinions could only have come from the external literature on nicotine.

Q: Dr. Rowell, have you reviewed U.S. Exhibit 22,967, "Motives and Incentives" written by Philip Morris scientist William Dunn?

A: I have.

Q: Dr. Henningfield cites this document to show that Defendants knew that cigarettes were a delivery device. What is your analysis of this document?

A: On the next page of the document, not cited by Dr. Henningfield, the Philip Morris scientist explains his comments about delivery devices.

> "Lest anyone be made unduly apprehensive about this drug-like conceptualization of the cigarette, let me hasten to point out that there are many other vehicles of sought-after agents which dispense in dose units: wine is the vehicle and dispenser of alcohol, tea and coffee are the vehicles and dispensers of caffeine, matches dispense dose units of heat, and money is the storage container, vehicle and dose-dispenser of many things."

Furthermore, this industry conference wasn't a secret. The last page of the Dunn document makes it clear that the conference papers were published as a book entitled, "Smoking Behavior: Motives and Incentives", published by V. H. Winston & Sons." Certain chapters of this book have even been cited in Surgeon General Reports. It was not secret science.

(2) Company Documents on Tar/Nicotine Ratios

Q: What do internal company documents from 1964 to 1988 indicate about the companies' attention to tar/nicotine ratios?

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A: Many of the tobacco company documents I read deal with the issue of tar levels and tar/nicotine ratios in cigarette smoke. My understanding from reading the documents is that the tobacco companies were attempting to respond to the health concerns about cigarette smoking which followed the 1964 Surgeon General's Report on smoking and health. There are frequent references to health issues and efforts by the industry to develop a low tar or "low delivery" product. The documents show that simple tobacco reduction, ventilation and/or filtering procedures, which decrease both the tar and nicotine levels in concert, make some "low delivery" cigarettes unacceptable to many smokers. There was a realization that nicotine is an important component of cigarette smoke, and many documents address the issue of cigarette "impact" and other sensory effects in the throat and airway, which are the result of nicotine in the smoke.

Q: Can you cite examples of a company document concerned with tar/nicotine ratios during this period?

A: There was research done by BATCo in the late 1970s and early 1980s on modified tar ratio cigarettes, as reflected in JD-010952 and JD-010887. Some of this work was done in collaboration with Dr. Russell. Research found that experimental cigarettes with low tar/nicotine ratios had unbalanced flavor characteristics as well as impact and irritation that were too high.

Q: Do you recall Dr. Farone's testimony regarding Lorillard's Nicotine Augmentation Project?

A: Yes. Dr. Farone testified that "Lorillard had a series of research projects, mostly in the 1980s, called the Nicotine Augmentation Project, also known as "NAP", that looked at ways to increase the delivery and effects of nicotine," and he cited several research memoranda from the Nicotine Augmentation Project.

Q: Are you familiar with Lorillard's NAP research?

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A: I have reviewed various NAP research memoranda, including many of those cited by Plaintiff's experts.

Q: Have you reviewed any documents or scientific literature that help explain why Lorillard undertook the NAP?

A: Yes. Both the internal Lorillard documents describing the NAP research and statements made in the scientific literature provide insight into Lorillard's reasons for undertaking the research carried out in the Nicotine Augmentation Project.

Q: Let's start with Lorillard's internal company documents – what do they say about Lorillard's reasons for undertaking the NAP research?

A: The documents state that Lorillard was undertaking the project in response to recommendations from "health-oriented-agencies". For example, an important memorandum relating to Nicotine Augmentation Project, dated May 4, 1976, U.S. Ex. 34,194, says: "Recommendations from health oriented agencies and pressure from competitive companies make it imperative that Lorillard develop a flavorful cigarette delivering lower tar while at the same time delivering a level of nicotine higher than could be obtained normally by conventional cigarette construction."

Q: How do you know this document marked the beginning of the Nicotine Augmentation Project?

A: It describes the purpose of the project, and lays out how the project will be pursued. In addition, it is the earliest document I have seen relating to the Nicotine Augmentation Project.

Q: Are there other internal Lorillard documents that provide the same rationale for the initiation of the project?

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A: Yes. For example U.S. Ex. 85,457, written approximately nine months after the NAP began, states: "The Nicotine Augmentation Project was undertaken to investigate ways to increase the nicotine to tar ratios of cigarette smoke. Health authorities have suggested that a low tar cigarette which gives an increased yield of nicotine would be advantageous, since the smoker could satisfy his urge for nicotine while inhaling lesser amounts of tar."

Q: Both of the company documents you mentioned indicate that individuals outside the company had recommended that the cigarette companies try to produce cigarettes with low tar but medium nicotine levels; are you aware of such recommendations being made prior to the initiation of the NAP?

A: Yes. As I said earlier, as early as 1964 in the report on Research into Smoking and Health, JE-034739, and certainly by 1975, with the publication of the Ashton & Watson publication on compensation and the publications of Dr. Russell, this would explain statements made by outside researchers at the time also help explain why Lorillard undertook the Nicotine Augmentation Project.

Q: Do any of the NAP research documents suggest that Lorillard conducted the NAP research in an effort to addict smokers, rather than in effort to respond to public health recommendations regarding safer cigarette design?

A: No. The documents indicate that the project was initiated in response to public health recommendations from those outside the industry. I haven't seen any internal documents that suggest Lorillard's NAP was undertaken in an effort to addict smokers.

Q: Do you know whether any of the cigarette design ideas that were researched in the Nicotine Augmentation Project were ever commercialized?

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A: No. I am not a cigarette designer. I don't know whether Lorillard ever incorporated any of the NAP research into a commercial product. I do know that the documents indicate that Lorillard encountered various difficulties in the research, including consumer acceptability problems and technological or manufacturing difficulties, that may have prevented commercialization.

Q: During his live testimony, Dr. Farone testified that he applauds Lorillard for undertaking the research carried out in its Nicotine Augmentation Project. Do you agree that it was reasonable for Lorillard to conduct nicotine augmentation research?

A: Yes. I believe it was reasonable for Lorillard to conduct this research, in light of the recommendations from public health-oriented groups and researchers.

Q: Was the Lorillard research novel?

A: No. As I have testified, the public research community was exploring tar/nicotine ratios and safer cigarettes generally.

(3) Dr. DeNoble's Research

Q: The Government presented testimony of two former Philip Morris scientists, Dr. Victor DeNoble and Dr. Paul Mele, in which they described certain nicotine research they had performed at Philip Morris in the early 1980's. Have you reviewed that testimony?

A: Yes.

Q: Dr. DeNoble testified that by the 1960's, Philip Morris researchers knew that nicotine affects the brain. Was that, or was that not generally known in the scientific community in the 1960's?

A: It was known. As I have noted, the 1964 Surgeon General Report discussed the central nervous system effects of nicotine.

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Q: Dr. DeNoble testified that his experiments at Philip Morris improved on the methods for conducting rat "self-administration" research; demonstrated that rats would self-administer for nicotine; showed that nicotine was a "weak reinforcer" when delivered intravenously; and that these tests were not intended to test whether nicotine is addictive. Do you agree or disagree with those assessments?

A: Yes, I agree. In particular, the data showed that, as Dr. DeNoble himself stated, "compared to other drugs that are self-administered, such as cocaine and amphetamine, rats will not work as hard to get a dose of nicotine" even when administered intravenously. While the technique they used to do the self-administration tests was an advance, the finding that nicotine was a weak reinforcer was already well-known in the published literature. So all that was new was an improved method for doing such research.

Q: Drs. DeNoble and Mele also testified that their research demonstrated that rats developed tolerance to nicotine; that "previous reports had demonstrated nicotine tolerance," and that no changes in behavior of the rats were observed when nicotine was taken away. Do you agree with those assessments?

A: Yes. The finding of tolerance had been demonstrated previously, and research with rats had shown that removal of nicotine did not have an adverse effect on behavior, i.e., there was no withdrawal syndrome.

Q: Dr. Mele testified that it was a new finding, based on their research, that tolerance to nicotine in rats had both physiological and behavioral components. Do you agree that this was new information as of the early 1980's with respect to nicotine tolerance?

A: No. Tolerance to nicotine in rats and humans had already been demonstrated.

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Q: Now Drs. DeNoble and Mele also testified about some research they conducted with respect to acetaldehyde and its interaction with nicotine. Did you review that?

A: Yes.

Q: What is the significance of these experiments with nicotine and acetaldehyde?

A: While the research suggested that nicotine with acetaldehyde boosted the reinforcement effect, they also found that removal of the combination of nicotine and acetaldehyde did not result in any withdrawal symptoms, and hence there was no physiological dependence from the two. As I have stated--and I believe both Drs. DeNoble and Mele agree--reinforcement alone does not equate to dependence, and with the absence of withdrawal symptoms, the finding of an additive or synergistic effect of nicotine and acetaldehyde, even if confirmed, would not be indicative of dependence, or even increased dependence compared to nicotine.

Q: What is your bottom line on the nicotine research done by Drs. DeNoble and Mele?

A: Apart from a somewhat improved method of performing intravenous self-administration studies, the research results themselves only confirmed what was already known in the published scientific literature.

2. Published Research and Company Documents on pH and Nicotine Absorption

Q: In the period between 1964 and 1988, was there external research concerning the form of nicotine taken into and distributed in a smoker's body?

A: Yes. During this period, there was recognition that the oral absorption of nicotine in the mouth is pH dependent, as seen in a 1970 article by Armitage and Turner, JD-000292. Moreover, there was also recognition that the rate or extent of nicotine absorption from the lung is not shown to be significantly affected by the pH of the smoke, as seen in a 1975 Armitage article, JD-011695.

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Q: Was this view sound?

A: Yes. First, in the lung, the pH is maintained in a very narrow range of 7.4 by the large buffering capacity of the alveolar fluids. Because of that set pH and the overwhelming amount of fluid in surface area of the lung, by the time the smoke gets down into the lung the nicotine is buffered to the lung's natural pH regardless of the smoke pH. The only likely effect of changing pH is a sensory effect. In fact, because the pH of all commercially available cigarettes is actually lower than the pH of the lung, it would not be possible to raise the lung pH to increase nicotine transfer, even if that were possible, which it is not.

Second, the pH of all cigarette smoke is more acidic than the body's natural pH so that cigarette smoke with or without ammonia cannot make a meaningful difference in the form or absorption of nicotine at biological tissue.

Third, since the chemical equilibrium between the different forms of nicotine maintains itself on a time scale of microseconds, any diffusion of uncharged nicotine across biological membranes would immediately result in more uncharged nicotine becoming available. Thus, the absorption of nicotine from cigarette smoke is dependent on the total concentration of nicotine reaching the lung and transit time in the lung; not on the relative proportion of charged to uncharged nicotine in the smoke.

Fourth, having passed into the blood, nicotine exists in a set ratio of approximately 3:1 charged to uncharged. The pH of the smoke makes no difference in the speed of delivery to body tissues (brain or elsewhere) or in the ability of nicotine to interact with receptors.

Finally, and most importantly, the huge surface area of the lung and the buffering capacity of the alveolar fluid makes the pH of the smoke unimportant. The acidic pH of the smoke is overwhelmed by the more alkaline pH of the body fluids such that there would be no

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difference in the form, degree or speed of absorption of nicotine across the lung membranes. In fact, the large surface area of the lung appears to act as a depot for nicotine such that the rate of delivery to the blood occurs rather slowly with no high peak blood levels being achieved.

Q: Dr. Rowell, to what extent has the pH of tobacco smoke been researched?

A: The pH of tobacco smoke has been researched, and publication of research findings in this area go back more than 50 years.

Q: Was this topic also addressed in internal company documents that you have reviewed?

A: Yes, it was.

Q: Let's talk first about the effect of pH on the perceived "strength" of tobacco smoke. When were research findings regarding this topic first published?

A: In 1929, Vickery and Pucher published that "[t]he determination of the free nicotine, as this volatile part of the nicotine has been designated, is of some importance in the chemical examination of tobacco, since the harsh flavor of certain tobaccos has been attributed to a high proportion of this component." (JD-010910)

In 1953, A.A. Schmuk published an authoritative volume entitled The Chemistry and Technology of Tobacco (JD-010914). There, at page 8, he noted: "The taste strength of cigarette tobaccos is closely dependent on the reaction of the tobacco smoke. The taste sensation is always stronger when tobacco alkalinity is higher; acid smoke does not produce a strong taste sensation but only a slightly sharp or a faint burning taste . . . . It is necessary to remember that the taste strength of tobacco is not identical with its physiological strength, the latter being determined by the nicotine content of the tobacco." Schmuk recognized at page 10 that the amount of "free" or "extractable" nicotine in smoke depended on pH: "The term 'free nicotine'

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is used in regard to that form of nicotine in tobaccos which may be steam-distilled or extracted by organic solvents without application of alkali. . . . Free nicotine corresponds to these easily hydrolyzable nicotine salts in tobacco. The poorer the taste quality of the tobacco the greater its content of free nicotine. Consequently, this form of nicotine corresponds to the taste strength of the tobacco."

Q: Did you see reference to this same concept in the internal company documents that you have reviewed?

A: Yes, I have. In the mid-1960s, BATCo appears to have conducted work with panels of smokers and, in the documents describing the findings also recognized that the pH of the smoke correlated to the perceived "strength" of the smoke. For example, in 1965, J.D. Backhurst of BATCo wrote that "[c]igarettes which give smoke of different pH levels and consequently varying amounts of 'extractable nicotine' have been examined by a Smoke Panel. First results suggest that the response of a smoker to the 'strength' of a cigarette is not related to the total nicotine content of the smoke but to the amount of 'extractable nicotine. . . . The reaction of a smoker to nicotine has been defined in some contexts as 'strength' of the smoke, or as throat irritation, or even as physiological response. These reactions do not necessarily parallel the nicotine delivery since a cigarette with a low nicotine yield may produce a greater response than a cigarette with a high one." (US-58625) In 1966, Backhurst wrote: "It was shown in an earlier report that the reaction of a smoker to the strength of the smoke from a cigarette could be correlated to the amount of 'extractable' nicotine in the smoke, rather than to the total nicotine content. This relationship has now been confirmed by an examination of further samples of cigarettes. . . . In general, people appear to find it difficult to inhale smoke which has a high 'extractable' nicotine content. . ." (US-46420)

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Q: Was work also done regarding the effect of pH on absorption of nicotine from cigarette smoke?

A: Yes.

Q: What was published in this regard?

A: Researchers demonstrated that this greater "strength" was not due to greater absorption of nicotine in the lungs. They consistently found that virtually all (over 90%) of the nicotine in cigarette smoke in the lungs was absorbed, no matter what the pH. This is due to the huge surface area in the lung through which absorption may take place.

For example, the 1961 Larson text (JD-000500) noted at pages 7 and 8 that "[t]he more alkaline main-stream smoke of cigars contains part of the nicotine in free form, in contrast to the more acid main-stream smoke of cigarettes, and this free nicotine condensing with the water vapor was said to be absorbed almost quantitatively by the body of the smoker. By the nicotine 'shift' (proportion of nicotine in the free form), enough nicotine is absorbed, just by mouth smoking and without inhaling, to give the desired physiological effects; cigar-smoke, consequently, does not need to be drawn into the lungs, which would be unpleasant because of its alkaline reaction. . . . To sum up, the nicotine uptake by the organism depends not on the nicotine content of the smoked tobacco, but rather on such factors as the acidity or alkalinity of the tobacco smoke . . . ."

Similarly, Ashton and Stepney found in 1982 that "[t]he lungs have a vast surface area for absorption in the regions where thousands of small blood vessels course under the linings of the air sacs on which the smoke is drawn, and the surface fluids into which the nicotine dissolves are slightly alkaline. When cigarette smoke is inhaled, absorption of nicotine is therefore both efficient and rapid. It has been estimated that around 90 per cent of the nicotine present as

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inhaled smoke is absorbed." (JD-010890) And Dr. Henningfield published in 1984 that "[c]igarette tobacco, which is more acidic, due to a flue-curing process (pH levels about 5.5), is poorly absorbed unless inhaled. Apparently, due to the large surface area of smoke exposure to the capillaries, the pH value of inhaled smoke is not a major determinant of absorption of nicotine from inhaled smoke." (JD-010831)

Q: What did internal company documents show?

A: At BATCo, Backhurst found in 1966 (US-55968) that "[w]hen the smoke is taken into the lungs there is virtually complete retention of the nicotine for all cigarettes examined." Evelyn at BATCo wrote in 1967: "Experiments in R.& D.E. and elsewhere have shown that there is, for all practical purposes, complete absorption of nicotine in the lungs . . . of nicotine from the smoke of cigarettes having different proportions of extractable nicotine." (US-87125)

Q: Were governments and public health authorities also interested in the effects of pH on smoke quality?

A: Yes. Citing the well-known increase in "satisfaction" smokers receive from smoke of higher pH and the perception of increased "strength," government and public health authorities suggested increasing the pH of cigarettes to develop low delivery cigarettes that would be acceptable to consumers. In particular, Elson and Betts (JD-000753) theorized in the Journal of the National Cancer Institute in 1972 that if the benefits of nicotine could be achieved through greater "impact" in the throat, smokers would not inhale the smoke—and thus harmful tar—into the lungs: "We suggest that one indication toward less harmful smoking lies in the direction of decreased tar and nicotine content of the smoke together with a reduced acidity, so that a reasonable degree of 'nicotine satisfaction' can be achieved with minimum lung cancer risk from inhalation of carcinogenic tar. The possibility that this condition could be attained with low tar

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and nicotine cigarettes by a suitable filter together with small amounts of additives which progressively reduce the acidity of the smoke is being investigated."

Q: Dr. Henningfield has testified that U.S. Ex. 22,077, Brown & Williamson's "Handbook of Ammonia Technology" shows that Brown & Williamson understood ammonia's effect on nicotine and "the potential effect to enhance the addictive effect on the smoker." How do you respond to Dr. Henningfield's testimony?

A: The document cited by Dr. Henningfield does not refer to any effects of ammoniation on the smokers of cigarettes. It does not even discuss the transfer of nicotine to the smoker, let alone any "addictive effect." Dr. Henningfield confuses the effect that increased tobacco pH could have on the form of nicotine in smoke as opposed to transferring nicotine into a smoker's body. This confusion is also apparent in the citation in his testimony to U.S. 21,707, which also refers to an increase of nicotine transfer through ammoniation. While increased pH will affect the amount of free nicotine in smoke, and therefore increase the sensory impact of the smoke, it does not affect the amount of nicotine transferred through the lung into a smoker's body.

Q: Dr. Henningfield also testifies that U.S. 20,807, a Brown & Williamson document containing minutes from an "Ammonia Technology Conference" "indicated an effort to comprehensively understand the use of ammonia compounds in cigarette manufacturing as tools to increase nicotine transfer from the tobacco to the smoker." (Henningfield written direct, 75.) How do you respond to Dr. Henningfield's testimony?

A: The document cited by Dr. Henningfield does not support his testimony. It is clear from that document that the use of ammonia in tobacco blend was to improve cigarette taste. As is clear on the face of the document, "AT [ammonia technology] is the key to competing in smoke

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quality with PM worldwide. . . . Its widespread use by PM has led the consumer to associate AT with good tobacco taste."

Q: Are you familiar with the testimony of Dr. Wigand concerning ammoniation?

A: Yes.

Q: Dr. Wigand refers to the same document as Dr. Henningfield and maintains that the document expressly refers to "improved nicotine transfer" as an effect of ammoniation. Is that accurate?

A: No. The document does indeed refer to "improved nicotine transfer" as an effect of ammoniation, but this does not specifically refer to transfer from smoke through a smoker's lungs but rather from tobacco to the smoke. Moreover, in the 1970's, public health authorities including Gori, at the National Cancer Institute, as well as other researchers, were advocating use of increased pH to create more free nicotine in tobacco smoke as a means to decrease inhalation while making smokers more satisfied with lower tar cigarettes. The companies were not researching these issues for the purpose of determining whether and to what extent nicotine had dependence properties, but rather were relying on the base of existing research in order to improve on less hazardous cigarette design, following these suggestions from the public health community.

Q: Are you aware of any statements by company scientists that the transfer of nicotine in the lungs is not dependent on the pH of smoke?

A: Yes. A 1976 Reynolds document entitled "Some Effects of Smoking" by Murray Senkus, a Reynolds scientist, U.S. Ex. 48,076, states:

> Now let's look at the fourth step in smoking - the period during which the smoke is held in the lungs. During this period there is complete transfer of nicotine from tar to blood. Transfer of nicotine in lungs is not dependent on pH of smoke. The lung

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surface area is so tremendous that it simply overrides the pH of tar. It makes no difference whether the pH of smoke is low, as in the case of an all-flue-cured cigarette such as the Canadian or English brands, or whether the pH of smoke is high as in the case of an all-burley cigarette such as the French cigarette. There will be complete transfer of nicotine from the tar to the blood during the short time the smoke is held in the lungs regardless of pH.

3. Terminology Applied to Smoking Behavior

a. Terminology Used by External Scientists

Q: In the period between 1964 and 1988, what terminology was used in the published literature to describe smoking and how?

A: While, as I have already testified, the Surgeon General labeled smoking an habituation in 1964, later in the same year as the Surgeon General's Report, the World Health Organization began a trend away from use of this terminology in favor of the concept of "dependence." The term "dependence" became the term of choice in the years between 1964 and 1988 in much of the published science.

Q: Between 1964 and 1988, did all published scientists use the term "dependence"?

A: Certainly, some researchers continued to refer to "addiction," but documents representing the consensus of leading authorities on smoking behavior used the term "dependence," as seen, for example, in the publications of the World Health Organization.

Q: In 1964, how did the WHO define drug "dependence"?

A: As seen in JD-000770, the WHO defined drug dependence, in 1964, as "a state arising from repeated administration of a drug on a periodic or continuous basis." The WHO noted that the characteristics of dependence will vary with the agent involved.

Q: Which other authorities adopted the concept of "dependence"?

A: There are many examples of the shift in terminology, but one of the most notable is in the 1965 edition of the standard textbook in pharmacology, "The Pharmacological Basis of

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Therapeutics" edited by Goodman and Gillman, which is JD-001012. That text noted on page 286 that it was possible and indeed advantageous to define all known patterns of drug abuse without employing the terms "addict" or "addiction." Interestingly, however, the text recognized that the flawed terminology of "addiction" would not disappear from the Lexicon and so suggested a logical definition of addiction as viewed as "an extreme" on a continuum of involvement with drug use, referring in a *quantitative* rather than a *qualitative* to the degree of drug use.

Q: Did WHO include tobacco, in 1964, on its list of substances that produce dependence?

A: No. It was not until 1974 that the WHO included tobacco in its compendium of substances that produced "dependence." Even then, the WHO expressly treated tobacco as a special case, noting in JD-001022 that, unlike the dependence-producing substances listed in the rest of the WHO compendium, tobacco produced relatively small effects on the central nervous system, and little disturbance in perception, mood, thinking, behavior or motor function.

Q: Were there any publications during this period between 1964 and 1988, that still used the term "addiction" in reference to nicotine?

A: Yes. Perhaps the most widely read by the general public would have been the 1972 Consumers Union Report on Licit and Illicit Drugs, JD-010760. This contained a five-chapter section devoted to nicotine, including a chapter entitled "Nicotine as an Addicting Drug." The assertion, as stated in the Consumers Union Report, was that "cigarette smoking is an addiction to the drug nicotine, that the overwhelming majority of those who smoke more than a few cigarettes become addicted, and that relatively few addicts quit permanently." This publication

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was the first widely distributed report to characterize cigarette smokers as "addicts" and to ascribe the term "addiction" to the drug nicotine.

Q: Did the Surgeon General's Office comment on cigarette smoking and addiction in the 1970s?

A: Yes. In 1979, a Surgeon General's Report was published. This voluminous work, U.S. Ex. 64,071, reviewed all of the significant studies to date on both the health consequences of smoking as well as the factors contributing to the initiation and maintenance of smoking. In a consideration of the various models responsible for the smoking habit, it was concluded that neither a nicotine addiction hypothesis nor a more general social learning model could adequately explain tobacco use. In fact, the first sentence of the major chapter entitled "Behavioral factors in the establishment, maintenance and cessation of smoking" presents what would seem to be, a fairly noncontroversial position, namely that "Smoking is a behavior -- a highly complex act which is accompanied by certain cognitions and hedonic states and based on various biochemical and physiological processes."

Q: Did additional literature in the 1970s refer to nicotine as addictive?

A: Yes. One of these was the 1977 NIDA monograph entitled "Research on Smoking Behavior," JD-004169. In the overview chapter, Russell reiterated his position in the following paragraph:

> In essence, the term 'dependence' or 'addiction' refers to a state in which the urge or need for something is so strong that the individual suffers or has great difficulty in doing without it, and in extreme cases cannot voluntarily stop using it when it is available. Tobacco smoking clearly falls into this category, and few other forms of drug-taking are as addictive as the puff-by-puff shots of nicotine obtained by smoking cigarettes. Not with alcohol, cannabis and possibly even heroin is the addiction so easily acquired. For most people, to smoke cigarettes at all is to become

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dependent. Cigarette smoking is clearly a drug addiction problem."

Q.: Did NIDA make other comments about smoking and addiction?

A: Yes. In 1983, as shown in JE-058808, NIDA's Director, William Pollin, made a statement before Congress and in his opening sentence, he talked about the "addictive properties of tobacco smoking." Still, he used the term "addictive" only once in the course of his Congressional statement.

Q: Was Dr. Pollin's statement to Congress made as some sort of consensus statement in the scientific community?

A: No. Other NIDA documents reflect continuing discussion during this time period over the appropriate terminology to use.

Q: In the early 1980's, then, did NIDA refer to smoking as both dependence and an addiction?

A: Yes. However, it is clear from JD-012675, a record of the NIDA Working Meeting On Tobacco Use As An Addictive Process, that use of the term addiction was chosen not because of what NIDA called "semantic precision," but rather for "its visceral effect on the public and the pressure on lawmakers that will result."

Q: What organizations besides WHO, if any, use "dependence" in describing tobacco use between 1964 and 1988?

A: The American Psychiatric Association, known as "APA," has been among the organizations adhering to the dependence standard of terminology -- even today. The APA publishes the Diagnostic and Statistical Manual of Mental Disorders, called the "DSM," which is designed to represent the consensus of thinking both within the psychiatric community with respect to the diagnostic criteria for mental syndromes and disorders. Before 1980, the DSM

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specifically excluded tobacco as a dependence-producing drug, but in 1980, for the first time, the APA created a diagnosis for "tobacco dependence." The APA did not, in 1980 or in any subsequent DSM, label tobacco use an "addiction."

Q: How does the APA define "dependence"?

A: In 1987, the APA published the DSM-III-R, which incorporated the new concepts of drug dependence -- namely, that drug dependence was a multifaceted cluster of phenomena, that required multiple criteria for diagnosis. The APA recognized different degrees of dependency -- mild, moderate and severe.

Mild dependence was characterized by a few symptoms resulting in no more than mild impairment in occupational functioning or in usual social activities, whereas severe dependence was characterized by many symptoms resulting in marked interference with occupational functioning or with usual social activities. Moderate dependence was characterized by symptoms between mild and severe.

Q: Where would nicotine fall in the APA's degrees of dependence?

A: The guidelines contained in the descriptive narrative of the symptoms suggest that nicotine would be considered as having only mild, or at most moderate, dependence properties. Based on the characterization of addiction as a "severe" form of drug dependence, this would indicate that nicotine, while perhaps being considered a drug of dependence, was not considered a drug of addiction.

Q: Did the APA say anything specifically about tobacco or nicotine in the DSM III-R?

A: The APA made a special exception for nicotine, noting that because of the wide availability of cigarettes and the absence of a clinically significant nicotine intoxication syndrome, a rating of severe Nicotine Dependence did not require impairment in occupational or

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social functioning. The APA also acknowledged that nicotine does not cause intoxication or impairment.

Q: Are the APA definitions and criteria that you have discussed set forth in exhibits in this case?

A: Yes, Both DSM II and DSM III are exhibits in this case and are JD-001016 and JD-000992, respectively.

b. Terminology Applied in Company Documents

Q: Did the internal company documents from 1964-1988 reflect the "dependency terminology"?

A: Yes. During this time period, when "dependence" was the term of choice in scientific literature external to the companies, some company scientists discussed "dependence," and others, like outside researchers, continued to talk about "addiction." Documents referring to "addiction" reflect no science that was unknown to the public scientific community and reflect no research concerning the pharmacological effects of nicotine that was not also known to that community. All information to that effect came from reading the outside literature. As in the public literature, company documents continued to reflect ongoing research on smokers smoking for nicotine.

C. The Time Period Post-1988

Q: Let's turn your focus now to the last period of time that we are discussing -- the period beginning in 1988.

A: All right.

Q: What happened in 1988?

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A: In 1988, the U.S. Surgeon General published a Surgeon General Report entitled "Nicotine Addiction," U.S. Ex. 64,591, which changed the definition of addiction from the one used in the 1964 Report. Thus, the Surgeon General changed the standard definition of "dependence," indicating that it was synonymous with addiction. Under the new definition, the primary criteria for a substance to be "addictive" were: (1) highly controlled or compulsive use; (2) psychoactive effect; and (3) drug reinforced behavior. Moreover, the 1988 Report was the first document purporting to reflect the opinion of many researchers to adopt addiction as the term to apply to smoking behavior.

Q: After the 1988 SG's report, did researchers adopt the term "addiction"?

A: The year following the publication of the Surgeon General's Report, several articles appeared which suggested that the monolithic "nicotine addiction" hypothesis of cigarette smoking is a much too simple explanation for this complex behavior in which nicotine plays a significant, but not exclusive, role as shown in both Ashton and Golding (1989), JD-010727, and Warburton (1989), JD-010752. The following year, 1990, three respected scientists, Jaffe, Warburton and Collins, indicated that equating the effects and dependence potential of heroin and cocaine with that of nicotine is unwarranted shown in JD-001065, JD-065203, and JD-004608.

Q: Did the APA change the terminology that it applied to smoking after the 1988 Surgeon General's Report?

A: No. The APA did not follow the lead of the 1988 Surgeon General's Report in DSM-IV which was published in 1994 and is JD-000460 in this case. Instead, the APA stuck with "dependence" terminology. The word "addiction" is not found in DSM-IV, and it is not used to

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describe cigarette smoking or nicotine. Nicotine is not even classified as an intoxicant in DSM-IV, even though caffeine is so listed.

Q: Is "dependence" terminology still used, not only by the APA, but by others as well?

A: Yes, myself included.

Q: So is it fair to say that, even today, there is no single term that all apply to smoking behavior?

A: Yes.

Q: Does any public health authority use the terms applied by Dr. Benowitz -- "loss of control of substance" -- or the terms applied by Dr. Henningfield -- "substantial loss of control"?

A: Not that I am aware of.

Q: Do you agree with Dr. Henningfield that even today, there is not a uniform definition of addiction adopted by all scientists?

A: Yes.

IV. IS NICOTINE THE SAME AS HARD DRUGS?

A. The Pharmacology of Nicotine

Q: What are the physiological effects of nicotine?

A: Nicotine has been shown to have a number of physiological effects in humans and in animals, on both the central nervous system and the peripheral nervous system. Nicotine releases adrenaline -- the "fight or flight" hormone which increases heart rate. Nicotine inhibits weight gain; changes EEG patterns; improves learning and memory; and improves the ability to focus. Nicotine also stimulates muscles and sensory nerves.

Q: How does nicotine produce physiological effects?

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A: Nicotine affects a smoker by acting on nerve cells -- specifically by binding to the receptors on nerve cells.

Q: How does nicotine in inhaled cigarette smoke travel to the receptors on nerve cells?

A: Once cigarette smoke is inhaled, nicotine in the smoke is absorbed in the respiratory tract, primarily in the lung, and travels through the blood stream to different parts of the body. Nicotine acts on the human nervous system which can be divided into two parts: the central nervous system, comprised of the brain and the spinal cord; and the peripheral nervous system, including all other nerves in the body. Nicotine acts on both parts of the nervous system.

Q: How, specifically, does nicotine act on the brain?

A: The brain is composed of a complex network of nerve cells. Nicotine acts on these nerve cells through "receptors," which are protein structures attached to the nerve cells in the human body.

Q: What happens when nicotine acts on a nerve cell through a receptor?

A: A complex communication process in the nervous system ensues, in which nerves communicate through electrical and chemical signals. Electrical impulses travel along the nerve terminals to the nerve, but these nerves are not connected to one another. The impulses are carried from a nerve terminal to the next nerve through a chemical process at the synapse, called neurotransmission. Nerves communicate with each other through the release of neurotransmitters, which are chemicals, at the synapse. The neurotransmitter released from an "upstream" nerve terminal will bind with a receptor on the "downstream" nerve cell essentially getting a signal from nerve cell A to nerve cell B after traveling the short distance across the synapse.

Q: Let's focus on the receptors first -- is nicotine unique in acting on receptors?

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A: No, the fact that nicotine acts on receptors does not make nicotine unique. In fact, no external substance is needed to have an effect on receptors. Receptors exist for chemicals that occur naturally in the body. At the most basic level of human biochemistry, receptors are affected by many behaviors, including running/exercise, gambling, shopping, and spending time on the Internet. Many natural substances from food or plants act on receptors. Much of what we eat and drink -- acts on receptors.

Q: How does the nicotine in cigarettes act on receptors?

A: Nicotine acts through acetylcholine receptors, which have a variety of effects, including prompting release of neurotransmitters.

Q: Let's turn to neurotransmitters. What neurotransmitters -- chemicals, really -- function in the brain to carry signals between nerve cells?

A: There are many neurotransmitters in the brain. The most thoroughly investigated ones include acetylcholine, serotonin, norepinephrine, glutamate, GABA, adenosine and dopamine.

Q: How do neurotransmitters in the brain affect the body?

A: Neurotransmitters in the brain affect the body in different ways. For example, acetylcholine affects learning and memory; serotonin affects mood and sleep; norepinephrine affects alertness; glutamate produces excitation; GABA affects anxiety and inhibition; adenosine affects synaptic modulation; dopamine affects pleasure and reward.

Q: Does nicotine work on one specific neurotransmitter?

A: No. Nicotine has been shown to affect a number of different neurotransmitters, with very different functions. In this sense, nicotine is like caffeine. A variety of neurotransmitters are affected by both nicotine and caffeine: acetylcholine; serotonin; norepinephrine; glutamate;

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GABA; dopamine. Conversely, typical drugs of abuse are more focused on a single neurotransmitter system.

B. Nicotine Is Not Identical to Hard Drugs

Q: Dr. Rowell, do any documents that you have reviewed indicate that the tobacco companies ever believed that nicotine was the same as hard drugs, such as heroin or cocaine?

A: No. The industry believed that nicotine was very different from hard drugs. For example, in 1988, on behalf of the industry, the Tobacco Institute issued a press release a public document, U.S. Ex. 21,239, in which they noted that "[t]he claim that cigarette smoking is a drug addiction similar to cocaine or heroin use, or alcohol abuse, is unfortunate and unwarranted." I have not seen any internal company documents or research that would contradict this view.

Q: What has the U.S. Surgeon General said regarding similarities or differences between nicotine and hard drugs?

A: The 1988 Surgeon General's Report, U.S. Ex. 64,591, asserted that the pharmacologic and behavioral processes that determine tobacco addiction are similar to those that determine addiction to some hard drugs, such as heroin and cocaine.

Q: In your opinion, is nicotine categorized together with morphine-like opiods and other drugs, such as cocaine, as "addicting drugs" as asserted in the 1988 Surgeon General Report?

A: Nicotine is on the low end of the dependence spectrum, whereas drugs such as heroin and cocaine are on the high end, as demonstrated by significant lack of physiological reward, lack of pronounced neurotransmitter activity and lack of use by the general population in pure form.

Q: Does scientific data support your opinion?

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A: Yes. A number of scientific studies have compared nicotine to drugs of abuse and have reached the same conclusion.

Q: Is it possible to pharmacologically compare nicotine to drugs of abuse, such as heroin or cocaine?

A: Yes, one can compare the effect on a given neurotransmitter.

Q: What neurotransmitter is useful for a comparison?

A: The neurotransmitter that has been most closely associated with drug dependence is dopamine. Like many other substances, nicotine stimulates the release of dopamine in brain tissue.

Q: What is the scientific basis for linking nicotine and other substances to dopamine release?

A: Scientists began to evaluate nicotine's effect on dopamine release in the late 1960s; and then, during the late 1980s and early 1990s, several studies demonstrated a link between administration of nicotine and release of dopamine in the limbic system of the brain. The limbic system is a network of structures in the brain which is known to play a role in emotions. One part of the limbic system thought to be the "pleasure center" of the brain is known as the nucleus accumbens.

Q: When was research first published that demonstrated a link between nicotine and dopamine release in the nucleus acumbens?

A: The first published work on nicotine causing the release of dopamine in the nucleus accumbens came from me and my co-researchers in 1987. We reported that nicotine could release dopamine from the nucleus accumbens in rat brain tissue *in vitro*, or in laboratory tests on tissue taken from rats. This work, for the first time, focused on dopamine release at the nerve

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terminal, eliminating any response between two neurons. The concentrations used in our experiments corresponded to those in the blood of cigarette smokers. Our work is documented in JD-010743, a 1987 article by me and my colleagues entitled "Stimulation of [^{3}H]Dopamine Release by Nicotine in Rat Nucleus Accumbens."

Q: How is dopamine released in the brain by nicotine and by other substances, including drugs of abuse?

A: Nicotine increases dopamine levels in the nucleus accumbens -- the pleasure center of the brain, through acetylcholine receptors; caffeine increases dopamine levels through adenosine receptors. Conversely, cocaine and amphetamine, psychostimulant drugs with a high potential for abuse, also increase dopamine levels in the synapse, but through a much more pronounced mechanism. Cocaine blocks the removal of dopamine from the synapse thereby leading to high levels in the synapse. Amphetamine increases dopamine levels both by release from the terminal and blocking its removal.

Q: Have any comparisons been done between nicotine and drugs of abuse with respect to dopamine levels?

A: Yes. Researchers have done *in vivo* studies, meaning studies of brain tissue in living rats. Using a microdialysis technique, which involves inserting a tiny probe -- about the size of a human hair -- into the limbic system of freely moving rats, researchers in Italy were able to monitor the effects of nicotine on the rats' dopamine concentrations during spontaneous behavior. The Italian research is documented in published peer-reviewed studies in the European Journal of Pharmacology, JD-010744 and Nature, JD-010861.

Further work, using this same technique, including some by the same group of researchers, makes clear that nicotine does not increase dopamine concentrations in the limbic

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system nearly as much as drugs of abuse. This work is documented in published peer-reviewed studies in the Proceedings of the National Academy of Sciences (JD-010846); Nature (JD-010861); and Neuroscience Letters (JD-010849).

Q: What did the studies show to be the specific differences between nicotine and other drugs in their effects on dopamine levels?

A: As shown clearly in JDEM-010259, these studies show that amphetamine and cocaine enhanced dopamine concentrations by 600% and 350%, respectively. Morphine enhanced dopamine concentrations by more than 300%. Nicotine, on the other hand, enhanced dopamine concentrations only by about 90% ; and caffeine enhanced dopamine concentrations nearly as much as nicotine, approximately 70%. These results show that nicotine and caffeine affect the levels of dopamine in the synapse by a much smaller degree than the more prototypical drugs of dependence.

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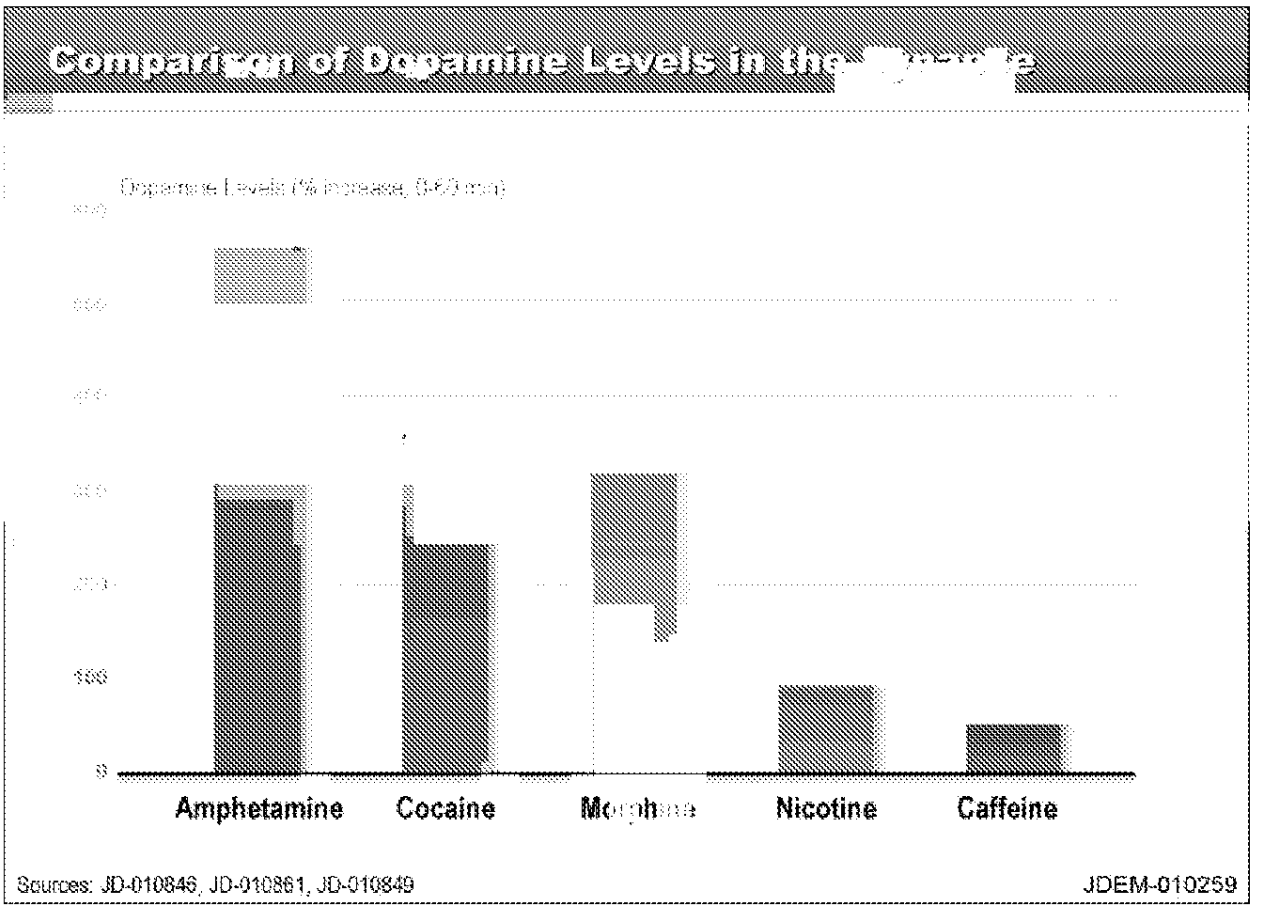

Q: Do people "like" using substances that produce higher dopamine concentrations better than those that produce lower dopamine concentrations?

A: At least one study, conducted by Dr. Jack Henningfield and identified in this case as JD-001042, has attempted to assess the reinforcing effects of different drugs in humans -- in other words, how much people like to take them.

Q: How did Dr. Henningfield conduct his study?

A: Dr. Henningfield gave different substances to a group of seven drug addicts, and measured their response. When he compared the "liking" scores -- measured by responses to the question "How good does this make you feel?" -- listed for various drugs to liking scores given

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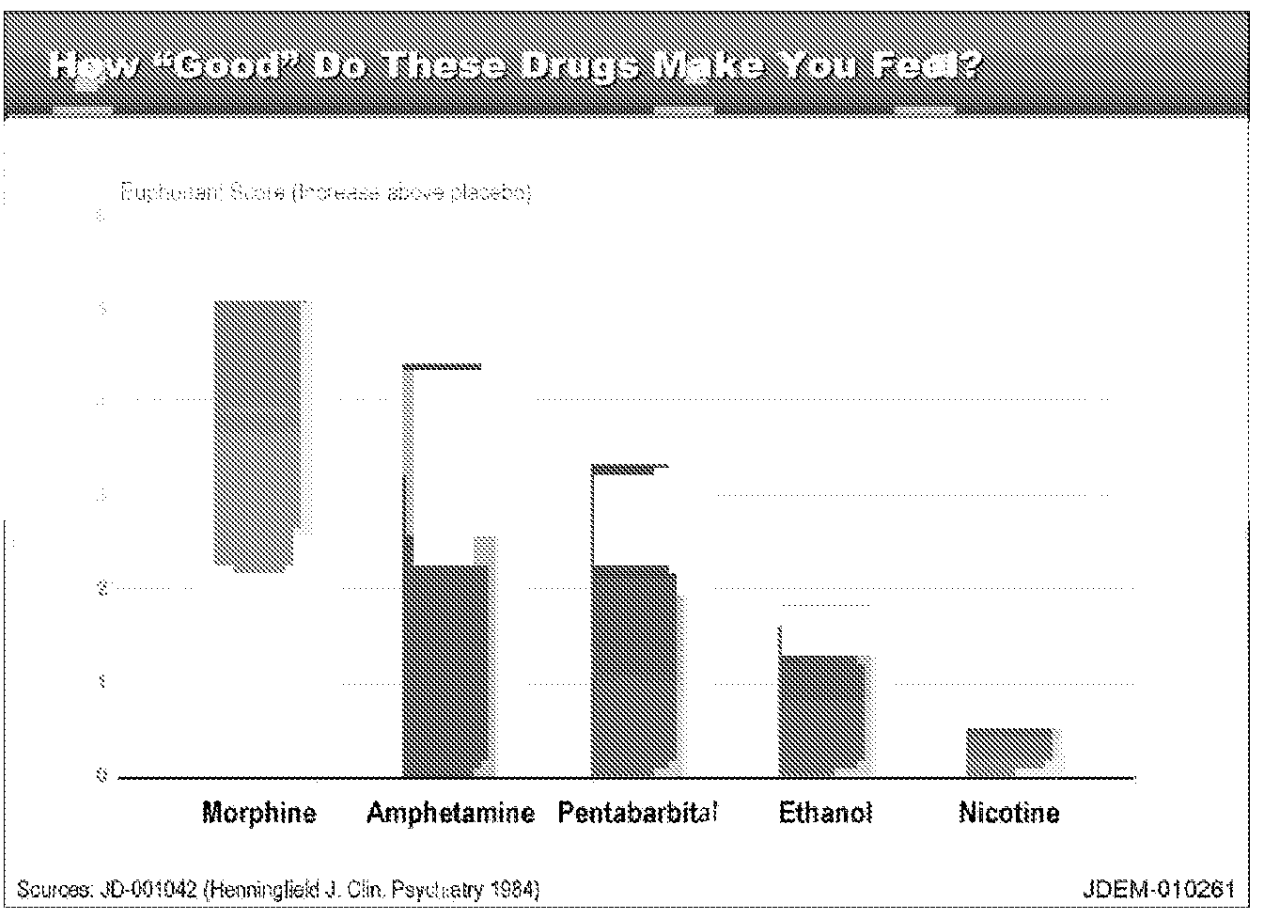
for "placebos" (saline injections), the disparity between nicotine and typical drugs of abuse is dramatic.

Q: Did Dr. Henningfield's study quantify the "liking scores" for nicotine and other drugs?

A: Yes. As shown in JDEM-010261, Dr. Henningfield's study quantifies the euphoriant scores above placebo for the following drugs: 5.0 for morphine; 4.3 for amphetamine; 3.3 for pentobarbital; 2.8 for ethanol (alcohol); and 0.5 for nicotine.



Q: You mentioned that Dr. Henningfield's study was an assessment of the "reinforcing" effects of different drugs in humans. What do the results of his study, then, indicate about the strength of nicotine's reinforcing effects?

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A: Nicotine is certainly a much weaker reinforcer than cocaine, morphine, and related classic drugs of abuse.

Q: How long has it been known that nicotine has some reinforcing effects?

A: Scientists have hypothesized for many, many years that nicotine has reinforcing effects. It was first scientifically demonstrated about 60 years ago in an article by Johnston, published in *Lancet*, which is JD-000972. The first nicotine administration studies in primates were actually done in the late 1960s, by Deneau and Inoki, JD-001014, but most of the studies have been done in the last 25 years.

Q: Aside from its weaker reinforcing effects, does nicotine otherwise differ from drugs of abuse in its pharmacological effect?

A: Yes. The characteristics of nicotine use differ greatly from drugs of abuse. First, there is no intoxication with nicotine, and intoxication itself is a reinforcing effect for some other drugs. Second, nicotine actually improves performance; and third, there is no severe physiological withdrawal from nicotine.

Q: Please explain the differences between nicotine and drugs of abuse with respect to intoxication.

A: First, it is important to distinguish intoxication from toxicity. Toxicity is produced by all drugs and medications at high doses, but this is not to be confused with intoxication as a physiological consequence of normal use. So, there is no intoxication from nicotine, while typical drugs of abuse -- heroin, cocaine, alcohol, amphetamines -- cause mental dysfunction in the user. The judgment and perception of a person drunk on alcohol or high on cocaine suffers as a result of the drugs they have taken. This is not true of users of nicotine or caffeine.

Q: Is there some "euphoria" associated with nicotine?

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A: Based on my research and published findings of other authorities on nicotine pharmacology, the mild "euphoria" associated with nicotine is not comparable to the intense euphoria from the prototypic drugs of abuse. The reinforcing effects of nicotine are more akin to those associated with normal behaviors, such as eating when hungry, drinking when thirsty, and sexual activity, opposed to the euphoria caused by other drugs. Furthermore, drugs such as cocaine, for example, cause an intense euphoria that makes users engage in binge activity.

Q: What other authorities, if any, in the field of dependence producing substances have published findings in agreement with your opinion in this regard?

A: Yes. For example, in JD-010701, an article by Dr. Jerome Jaffe, a leading authority on addiction issues, concludes that the absence of psychotoxicity of nicotine is a rational basis for distinguishing nicotine from other more severe forms of drug dependence. Similarly, in JD-010807, D.G. Gilbert, another researcher, found the reinforcing effects of nicotine to be more similar to caffeine and far less potent than "states of abnormal intoxication" associated with cocaine, heroin, and morphine.

Researchers have certainly documented the intense euphoria caused by cocaine that makes users engage in binge activity -- something not seen with nicotine. Cocaine addicts engage in compulsive, uncontrolled binge activity using cocaine at high doses to produce extreme euphoria. As described in JD-010786, an article entitled "Cocaine Dependence," addicts average three binges per week with each binge lasting from 8 to 24 hours. During binge activity, cocaine addicts ignore all activity unrelated to cocaine, including nourishment, sleep, survival, money, loved ones and personal responsibilities.

Q: Please explain the differences between nicotine and drugs of abuse with respect to performance.

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A: At the levels which occur in cigarette smokers, nicotine actually improves smokers' performance in certain respects: (1) Nicotine increases the speed and accuracy of information processing; (2) it improves ability to focus or "selective attention"; (3) it sustains vigilance; (4) and it has beneficial effects on learning and memory -- all demonstrated by Ashton and Golding, in JD-010727. Nicotine's ability to improve learning and memory have also been clearly shown in animal studies.

Nicotine can also act as a tranquilizer that reduces stress, anxiety and tension for many individuals according to experimental studies reported by Gilbert in JD-010807.

Q: Please explain the differences between nicotine and drugs of abuse with respect to withdrawal.

A: Nicotine does not produce severe physiological withdrawal in contrast to other drugs such as heroin, barbiturates, and alcohol, as seen on JDEM-010264, which summarizes many of the physiological effects of withdrawal from these substances.

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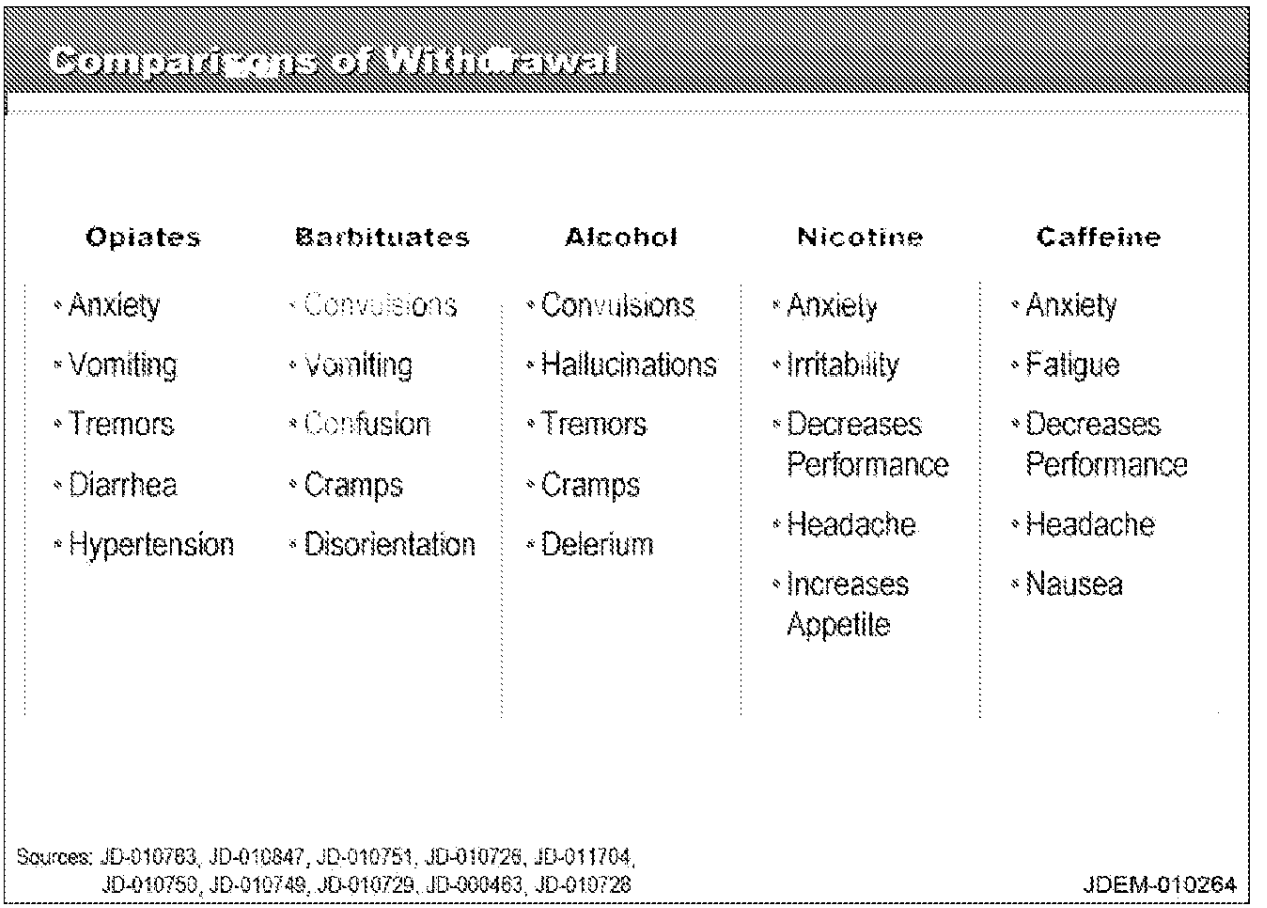

It is well established that heroin causes diarrhea, hypertension, tremors, uncontrollable muscular movements, and vomiting.

Similarly, barbiturates include the following withdrawal symptoms: abdominal cramps, confusion, disorientation, convulsions, life-threatening CNS depression, nausea, and vomiting.

Even ethanol (alcohol), a widely available legal product, causes the following severe withdrawal symptoms in addicts: convulsions, diarrhea, delirium, tremens, hallucinations (visual, tactile, auditory), psychosis, seizures, and vomiting.

In contrast, the most common and abundantly documented withdrawal symptoms of nicotine vary with the individual and do not constitute a defined abstinence syndrome. Those

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symptoms, while certainly discomfiting, are: impatience, irritability, anxiety, restlessness, headache, insomnia, decrease in mental efficiency, and increased appetite.

Q: Are these withdrawal symptoms documented in the published medical literature?

A: Yes. For heroin, I would direct you to Krystal, JD-010783; for barbiturates, I would direct you to Clark JD-010847; for alcohol, I would also direct you to Clark JD-010847; for nicotine, I would direct you to the following articles by Hughes: JD-010751; JD-010726; JD-011704; JD-010750; and also to Clark, JD-010847.

Q: Then, is nicotine withdrawal at all comparable to withdrawal from hard drugs?

A: No. The published authorities agree -- and I share their view -- that nicotine withdrawal is not comparable to withdrawal from hard drugs. The consensus is that tobacco withdrawal differs from other drug-withdrawal states in several ways. First, cessation of tobacco does not result in physical symptoms seen with other drugs. Second, other than hunger and a craving for tobacco, there is no protracted withdrawal syndrome. Third, in other drug-withdrawal syndromes, such as those seen with opioids or benzodiazepines, a medication that blocks that effect of the drug precipitates the withdrawal syndrome. This does not occur with tobacco withdrawal. So, authorities in the field recognize that tobacco withdrawal symptoms are not even close to the profile of withdrawal effects seen in other drug dependencies -- including alcohol.

Q: What authorities, in particular, have written on the differences between nicotine withdrawal and withdrawal from other drugs?

A: Both J.R. Hughes and R. Nil have written on this subject as seen in two publications: Hughes, "Tobacco: Withdrawal (abstinence) Syndrome," JD-010726; Nil, "A Psychopharmacological and Psychophysiological Evaluation of Smoking Motives," JD-010749.

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Q: Dr. Benowitz testified that the process of developing tolerance to nicotine occurs over a period of many years as a smoker transitions from experimenting to becoming a regular smoker. (Benowitz Written Direct, pp. 24-25.) Do you agree with Dr. Benowitz?

A: I cannot agree with Dr. Benowitz on this. It is certainly true that most smokers begin by smoking very occasional, and then generally increase their smoking over a period of many years to a plateau of "regular" smoking. In my opinion, this is not "tolerance" in the same sense as that term applies to hard drugs. There is nothing about nicotine that would require several years to develop tolerance to its mild pharmacological effects, and studies confirm that tolerance can easily be developed quickly -- within a matter of weeks. The fact that most smokers gradually increase their smoking over a period of years, without binging like users of drugs of abuse is consistent with the notion I have explained that it is smoking behavior, not just nicotine, which is critical in the development of cigarette smoking dependence.

Q: Can you summarize, generally, the differences between nicotine and caffeine, on the one hand, to typical drugs of abuse, on the other?

A: As shown in JDEM-010265, dissimilarity of both nicotine and caffeine to typical drugs of abuse, is quite apparent.

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Drug Comparisons

	Amphetamine	Cocaine	Morphine	Nicotine	Caffeine
Neurochemical Activity	High	High	High	Low	Low
Intoxication	Yes	Yes	Yes	No	No
Impaired Judgment	Yes	Yes	Yes	No	No
D.E.A. Controlled Substance	Yes	Yes	Yes	No	No

JDEM-010265

First, administration of amphetamine, cocaine, and morphine results in high neurochemical activity, as assessed by their effect on dopamine in the brain. In contrast, administration of nicotine and caffeine results in low neurochemical activity. Second, administration of amphetamine, cocaine, and morphine results in specific stimulation of neurotransmitter systems whereas administration of nicotine and caffeine results in non-specific modulation of neurotransmitter systems. Third, amphetamine, cocaine, and morphine result in intoxication and impaired judgment, while nicotine and caffeine do not have these effects. Finally, amphetamine, cocaine, and morphine are of such magnitude for drug dependence that they are controlled under the most strict Schedule I and II of the Schedule of Controlled

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Substances by the Drug Enforcement Administration. Nicotine is not a controlled substance at all.

Q: Can you summarize the difference between nicotine and caffeine, on the one hand, and typical drugs of abuse, on the other with respect to dependence?

A: The difference between nicotine and caffeine, on the one hand, and typical drugs of abuse on the other, is well recognized by pharmacologists and can also be shown by charting reward and psychological dependence; physiological dependence; and status as a controlled substance, as shown in JDEM-010263.

Dependence Potential of Drugs

Drug	Reward and Psychological Dependence	Physiological Dependence
Morphine, Heroin	Strong	Very Strong
Methadone	Less Strong	Strong
Alcohol	Moderate	Moderate
Cocaine	Strong	Weak
Amphetamine	Strong	Weak
PCP (Phencyclidine)	Moderate	Weak
Barbiturates	Weak	Strong
Nicotine	Weak	Weak
Caffeine	Weak	Weak

Sources: JD-010848 JDEM-010263

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The chart demonstrates that only nicotine and caffeine are weak in both psychological and physiological dependence, and only nicotine and caffeine are not controlled substances, from a laundry list of drugs.

Q: On what data do you base this chart?

A: This chart is based on information in JD-010848, a publication entitled "Drug Dependence and Drug Abuse."

Q: Where should nicotine be placed in the context of drug dependence?

A: In answering this question, it is crucial to distinguish between "nicotine" as a drug and "cigarette smoking" as behavior. The evidence to date indicates that pure nicotine is very much on the low end of the spectrum for the potential for drug dependence: First, there are studies that I will discuss in detail later in this examination where nicotine was injected intravenously and failed to produce consistent marked euphoria or other strong rewarding or reinforcing effects. Second, as I have discussed, nicotine's effect in neurochemical studies measuring such things as dopamine release indicates that its actions are weak compared to drugs with high dependence potential. Third, there are no reports that individuals administer pure nicotine -- which is available -- by any route. Fourth, there is no evidence of significant nicotine cravings in individuals to which pure drug has been administered.

Q: To what, then, do you attribute smokers' difficulty in quitting?

A: Cigarette smoking is a complex, very compelling, and highly conditioned behavior. Social interactions, environmental and sensory stimuli, habituation, personality, and genetic factors all play a part. Cigarette smoking can be considered largely a behavioral dependence, reinforced and complimented by the weakly dependence-producing drug, nicotine. To consider a

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cigarette as just a nicotine delivery device is both simplistic and ignores the basic facts. Cigarette smoking is not simply a drug addiction.

Q: Does the fact that nicotine differs from hard drugs mean that it is easy to quit?

A: No.

Q: For how long has it been known that it is difficult to quit smoking?

A: It has been recognized for centuries that, for many people, the use of tobacco products can lead to craving and difficulty in giving up the habit. In fact, in the mid-1800s, Mark Twain joked about how hard it was to quit smoking, saying, "It's easy . . . I've done it a hundred times."

Q: Is there any pharmacological reason that smoking cessation is difficult?

A: No. The pharmacological effects of nicotine are relatively weak as discussed earlier in my examination. In my opinion, the difficulties encountered in smoking cessation are largely caused by difficulties in ceasing a complex behavior that itself is compulsive, ingrained, and highly conditioned in many smokers.

Q: Is the long-known fact that smoking cessation is difficult any different from Dr. Benowitz's definition of "drug addiction" as a "loss of control of drug taking behavior" (Benowitz Written Direct, p. 26) or Dr. Henningfield's definition as "the difficulty to stop in the face of harm or sometimes expressed as the relative loss of control?"

A: I have no disagreement with Dr. Benowitz's or Dr. Henningfield's definition of "drug addiction" as "loss of control of drug taking behavior." If Dr. Benowitz or Dr. Henningfield wish to define "behavioral addictions" as a "loss of control over the behavior," then I agree that the difficulty many cigarette smokers have in quitting would qualify cigarette smoking as an addiction, in the same sense that there are other behavioral addictions.

Q: Is cigarette smoking merely the delivery of nicotine?

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A: No. It is important to distinguish between nicotine as a drug and cigarette smoking as a behavior. First, as a pharmacologist, I clearly understand that dependence is a concept that applies to the effect of drugs on an organism. Second, as discussed previously, cigarette smoke cannot rightly be considered a drug because it is composed of literally thousands of distinct and identifiable substances. Third, one substance in cigarette smoke is nicotine. But as described earlier in my testimony, cigarette smoking behavior consists of more than just the delivery of nicotine

In 1979, the Surgeon General properly described cigarette smoking when he wrote: "Smoking is a behavior -- a highly complex act which is accompanied by certain cognitions and hedonic states and based on various biochemical and physiological processes." (1979 Surgeon General's Report at 16-5 (U.S. Ex. 64,071).

Q: Do behaviors, such as the behavior of cigarette smoking, have an effect on the central nervous system, and on reward centers specifically?

A: Yes. Using the same microdialysis technique described earlier to compare nicotine with other drugs, researchers have measured the effect of several behaviors on dopamine release in the nucleus accumbens. The data show that behaviors can affect dopamine concentrations more than either nicotine or caffeine. Researchers have compared dopamine release for behaviors ranging from smoking, to ingestion of food when hungry, water when thirsty or to sexual behavior, as shown in JDEM-010260.

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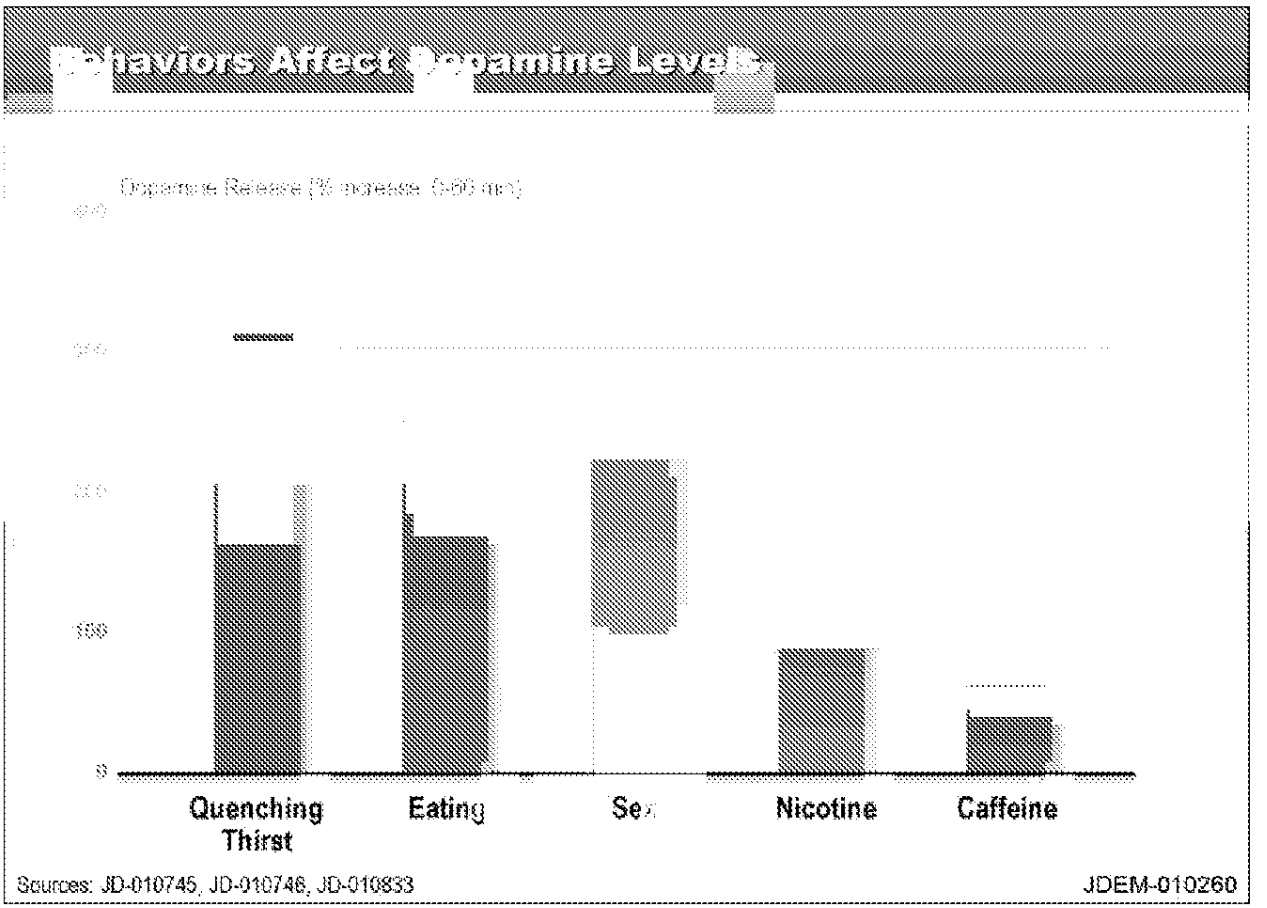

The results of this research in experimental animals show that nicotine increased dopamine by a factor of about 90%, while caffeine increased it by approximately 70%; consumption of a chocolate flavored liquid diet to hungry animals increased dopamine release by 250%; water given to thirsty rats increased dopamine release over 330%; and sexual behavior increased dopamine release more than 230%.

Q: What research supports the graph shown in JDEM-010260?

A: A number of studies support the graph, including: Wilson, JD-010745; Young, JD-010746; and Damsma, JD-010833.

Q: Has any research ever separated the effects of nicotine from the behavioral reinforcement of smoking?

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A: Yes. Studies by a leading researcher in the area of nicotine's effects on smoking behavior, Dr. Jed Rose, separated the effects of nicotine from the behavioral reinforcement of smoking. Dr. Rose showed that the effects of nicotine can be separated from the effects of smoking through a blind experiment in which people were given nicotine without smoking or smoking without nicotine. His work supports my conclusion that smoking behavior is driven by much more than nicotine and in fact shows that at least in the short term, the behavioral component of cigarette smoking is more important than nicotine delivery to the smoker. Dr. Rose's work is documented in JD-010809, "Comparative Effects of Intravenous Nicotine and De-Nicotinized Cigarette Smoke" and in JD-001218, the published peer-reviewed article that was published after I had identified the abstract of the study for my reliance list.

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